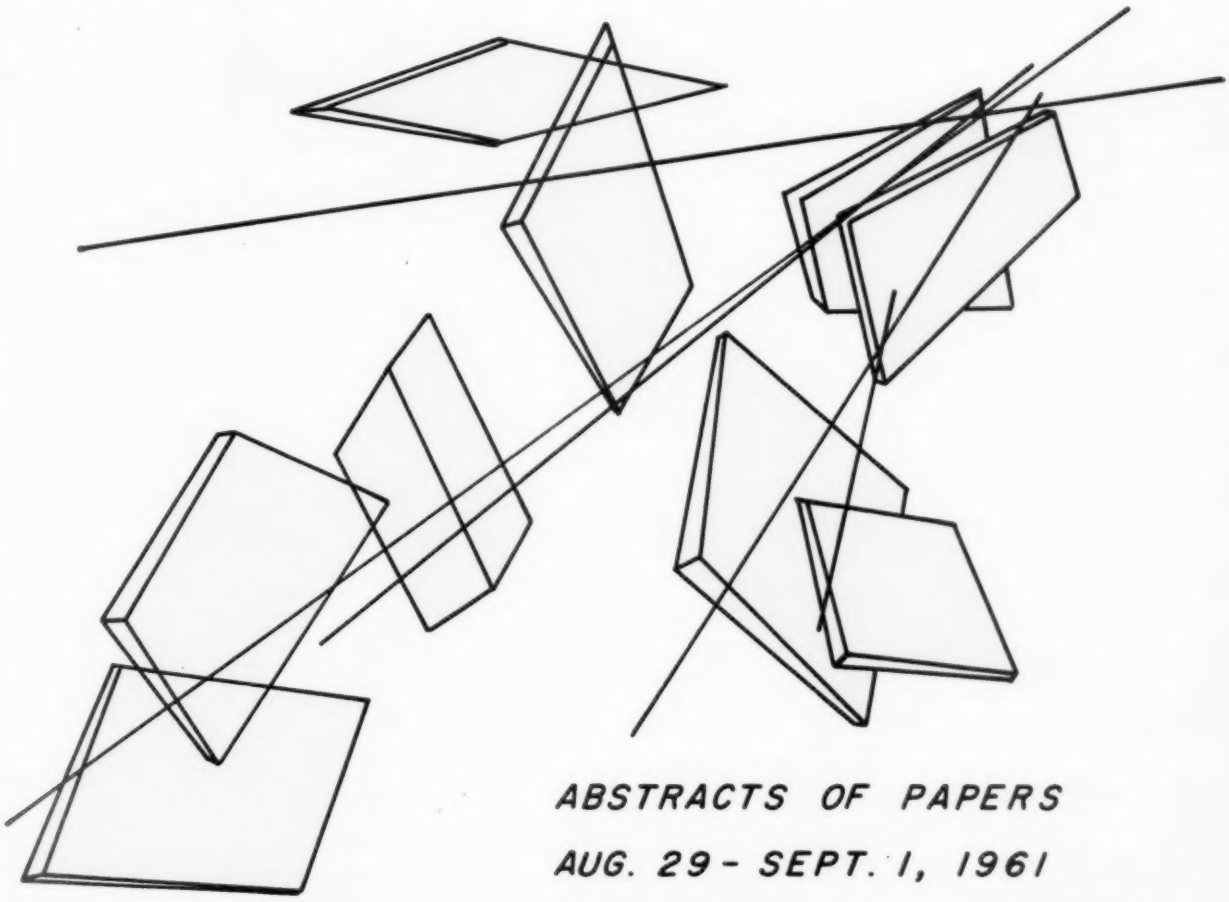
FALL 1961

THE PHARMACOLOGIST



ABSTRACTS OF PAPERS
AUG. 29 - SEPT. 1, 1961
ROCHESTER, N. Y. MEETING

Vol. 3, No. 2

THE AMERICAN SOCIETY FOR PHARMACOLOGY
and
EXPERIMENTAL THERAPEUTICS, INC.

Beaumont House Washington, D. C.

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Additional copies of this issue may be obtained from Dr. H. George Mandel, George Washington University, School of Medicine, 1335 H Street, N.W., Washington 5, D. C.

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

List of Officers
1961-1962

President:	Carl C. Pfeiffer (1962) New Jersey Neuro-Psychiatric Institute Princeton, New Jersey
President-elect:	H. B. van Dyke (1962) Columbia University College of Physicians and Surgeons New York 32, New York
Secretary:	H. George Mandel (1963) George Washington University Washington 5, D. C.
Treasurer:	Frederick E. Shideman (1962) University of Wisconsin Madison 6, Wisconsin
Treasurer-elect:	James A. Bain (1962) Emory University Atlanta 22, Georgia
Past-president:	Alfred Gilman (1962) Albert Einstein College of Medicine New York 61, New York
Councilors:	Walter F. Riker, Jr. (1962) Cornell University Medical College New York 21, New York
	George H. Acheson (1963) University of Cincinnati Medical College Cincinnati 19, Ohio
	Lawrence Peters (1964) University of Kansas Medical Center Kansas City 12, Kansas
Executive Officer:	Ellsworth B. Cook 9650 Wisconsin Avenue Washington 14, D. C.
Historian:	E. M. K. Geiling

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

List of Committee Members and Society Representatives
1961-1962

Membership Committee
W. Clarke Wescoe (1962), Chairman
Robert F. Furchgott (1963)
John J. Burns (1964)

Finance Committee
James A. Bain (1964)
Allan D. Bass (1962)
Karl H. Beyer (1962)
Robert M. Featherstone (1964)
Otto Krayer (1963)
Frederick E. Shideman (1964), Chairman

Committee on Educational Affairs
Allan D. Bass (1963)
Avram Goldstein (1962)
Louis S. Goodman (1964)
Julius B. Kahn, Jr. (1964)
Thomas H. Maren (1962)
Edward W. Pelikan (1962)
Jurg A. Schneider (1963)
Klaus Unna (1963), Chairman
Daniel T. Watts (1963)
Fred W. Schueler (ex officio)

Nominating Committee
K. K. Chen, Chairman
Walter Booker
Keith F. Killam, Jr.
Paul S. Larson
Amedeo S. Marrazzi

Committee on Professional Affairs and Public Relations
Maynard B. Chenoweth (1963)
Ellsworth B. Cook (1964)
Carl A. Dragstedt (1964)
George E. Farrar (1962)
Nicholas J. Giarman (1963)
Harold C. Hodge (1962), Chairman
M. L. Tainter (1962)

Program Committee
Kenneth P. DuBois (1963)
Walter Modell (1963)
Fred W. Schueler (1962), Chairman
Henry H. Swain (1964)
Klaus Unna (ex officio)

Representative to the Public Information Committee of the Federation
Frank C. Ferguson, Jr. (1963)

Representatives to the Council of A.A.A.S.
James A. Bain (1962)
Albert J. Plummer (1963)

Representatives to the National Research Council
John C. Krantz, Jr. (1962) (Division of Medical Sciences)
Walter M. Booker (1962) (Division of Biology and Agriculture)
John J. Burns (1963) (Division of Chemistry and Chemical Technology)

Representatives to the International Union of Physiological Sciences
K. K. Chen (1963)
Otto Krayer (1965)
Carl F. Schmidt (1967)
James A. Shannon

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

Editorial Boards
1961-1962

Editorial Board, Journal of Pharmacology and Experimental Therapeutics

Editor: Lawrence Peters*
Assistant Editor: Marion deV. Cotten
Index Editor: R. M. Isenberger

Specific Field Editors:
R. P. Ahlquist, Autonomic Pharmacology
H. L. Borison, Neuropharmacology
J. J. Burns, Drug Metabolism and Disposition
M. deV. Cotten, Cardiovascular Pharmacology
P. B. Dews, Behavioral Pharmacology
Avram Goldstein, Biochemical and Cellular Pharmacology
Louis Lasagna, Clinical Pharmacology
G. H. Mudge, Renal Pharmacology and Electrolytes

Julius Axelrod	H. C. Hodge	F. W. Schueler
H. K. Beecher	D. J. Jenden	A. M. Shanes
E. F. Domino	K. F. Killam, Jr.	P. A. Shore
W. W. Douglas	J. P. Long	C. C. Smith
K. P. DuBois	H. G. Mandel	J. L. Strominger
Sydney Ellis	T. H. Maren	H. H. Swain
J. R. Fouts	P. L. Munson	E. Leong Way
M. E. Friedkin	Barbara R. Rennick	T. C. West
R. F. Furchgott	W. K. Riker	E. J. Walaszek
L. I. Goldberg	Jay Roberts	D. J. Woodbury
P. B. Hagen	P. R. Saunders	L. A. Woods
		J. A. Zapp, Jr.

*Will be replaced on October 1, 1961 by Neil C. Moran.

Editorial Board, Pharmacological Reviews

George B. Koelle, Chairman

George H. Acheson	G. A. H. Buttle	Frederick S. Philips
H. Blaschko	Erik Jacobsen	Börje Uvnäs
A. S. V. Burgen	Seymour S. Kety	Marthe Vogt

Editorial Advisory Board, Pharmacological Reviews

Adrien Albert	B. B. Dikshit	I. R. Innes
F. von Brücke	Pietro Di Mattei	J. Jacob
K. Bucher	Fernando Peres Gomes	J. Mardones R.
J. A. Cohen	P. Holtz	H. Yamada

Board of Publications Trustees

Otto Krayer (1962), Chairman

Karl H. Beyer (1964) George B. Koelle
Lawrence Peters (1963)

Secretary of Publications: Miss Eleanor Bates

The American Society for Pharmacology and Experimental Therapeutics, Inc.
extends congratulations and a hearty welcome
to its
NEWLY ELECTED MEMBERS

Anderson, Edmund G.
Argus, Mary F.

Becker, Bernard A.
Beem, John R.
Burack, Walter R.
Burkhalter, Alan
Buyske, Donald A.

Chappel, Clifford I.
Colville, Kenneth I.
Condouris, George A.
Conney, Allan H.
Cook, Ellsworth B.
Coret, Irving A.
Cummings, John R.

Dayton, Peter G.
Durham, William F.

Ellis, Charles H.
Ellman, George L.

Fisher, James W.
Fleisher, Joseph H.
Fleming, William W., Jr.
Freedman, Daniel X.

Gardier, Robert W.
Guth, Paul S.

Hagen, Jean H.
Harrisson, Joseph W. E.
Heimberg, Murray
Hollister, Leo E.

Irwin Richard L.

Jaffe, Julian J.

Keplinger, Moreno L.
Klein, Richard L.
Kuperman, Albert S.

Laties, Victor G.
Leiter, Joseph
Levy, Bernard
Lin, Tsung-min

Marshall, Jean M.
Matthews, Richard J., Jr.
Mautner, Henry G.

Nahas, Gabriel G.

Pindell, Merle H.
Plaa, Gabriel L.
Poutsiaka, John W.
Prusoff, William H.

Rosenberg, Philip
Roszkowski, Adolph P.

Salmoiraghi, Gian C.
Sheps, Mindel C.
Sigg, Ernest B.
Smith, Frank A.
Standaert, Frank G.
Stanton, Hubert C.
Stone, Joseph E.
Szara, Stephen I.

Takemori, Akira E.

Vogel, Adolph W.

Weiss, Bernard
Witkin, Lloyd B.
Wylie, David W.

The American Society for Pharmacology and Experimental Therapeutics, Inc.
acknowledges with grateful appreciation
its
CORPORATE ASSOCIATES

Abbott Laboratories, Incorporated
Alcon Laboratories, Inc.
Arnar-Stone Laboratories, Inc.
Astra Pharmaceutical Products, Inc.
Ayerst Research Laboratories
Baxter Laboratories, Inc.
Don Baxter, Inc.
Bristol Laboratories, Inc.
Burroughs Wellcome & Co. (U.S.A.) Inc.
Carworth Farms, Inc.
The Charles River Breeding Laboratories, Inc.
Chicago Pharmacal Company
CIBA Pharmaceutical Products, Inc.
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Hoffmann-La Roche, Inc.
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Johnson & Johnson
Knoll Pharmaceutical Company
Kremers-Urban Company
Lakeside Laboratories, Incorporated
Lederle Laboratories
The Lilly Research Laboratories, Eli Lilly and Company
Arthur D. Little, Inc.
Lloyd Brothers
Mallinckrodt Chemical Works
McNeil Laboratories, Inc.
Mead Johnson & Company
The Merck Company Foundation
Wm. S. Merrell Company
Miles Laboratories, Inc.
The National Drug Company
New Drug Institute, Inc.
The Norwich Pharmacal Company
Ortho Research Foundation
Parke, Davis & Company
S. B. Penick & Company
Chas. Pfizer & Co., Inc.
Pharmacology Research, Inc.
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Riker Laboratories, Inc.
A. H. Robins Company, Inc.
Sandoz Pharmaceuticals
Schering Corporation
G. D. Searle & Co.
Sherman Laboratories
Smith Kline & French Laboratories
Smith, Miller & Patch, Inc.
The South Shore Analytical and Research Laboratory, Inc.
The Squibb Institute for Medical Research
Sterling-Winthrop Research Institute
Strong Cobb Arner Inc.
Syntex Corporation
The Upjohn Company
Wallace Laboratories, Division of Carter Products, Inc.
Warner-Lambert Research Institute
Woodard Research Corporation
Wyeth Institute for Medical Research

ANNOUNCEMENTS OF COMING MEETINGS

Federation of American Societies for Experimental Biology:

1962: Atlantic City, N. J., April 16-20
1963: Atlantic City, N. J., April 15-19
1964: Chicago, Ill.
1965: Atlantic City, N. J.
1966: Atlantic City, N. J.
1967: Chicago, Ill.

Fall Meetings of The American Society for Pharmacology and Experimental Therapeutics, Inc.:

1961: Rochester, N. Y., August 29-September 1
1962: Nashville, Tenn. (Vanderbilt)
1963: San Francisco, Calif. (Univ. of Calif.)
1964: Little Rock, Ark. (Univ. of Arkansas)
1965: Philadelphia, Pa. (Univ. of Penna.)
1966: Mexico City (Univ. Nacional Autónoma de Mexico)

American Association for the Advancement of Science - Annual Meeting:

1961: Denver, Colorado, December 26-31

American Medical Association - Annual Meeting:

1962: Chicago, Ill., June 25-29

Third Inter-American Conference on Occupational Medicine and Toxicology:

1961: Coral Gables, Fla., August 6-10

First International Pharmacological Meeting:

1961: Stockholm, Sweden, August 22-25

XXII International Physiological Congress:

1962: Leiden, Netherlands, September 11-17

MINUTES OF COUNCIL MEETINGS
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Rooms #1 and #3, Dennis Hotel
Atlantic City, New Jersey

First Council Meeting: 9:00 a.m., Sunday, April 9, 1961
Present: Drs. Acheson, Beyer, Cook, Featherstone, Gilman (presiding), Goodman, Hodge (part time), Mandel, Pfeiffer, and Shideman.

Torald Sollmann Award Committee Meeting: Present: Drs. Acheson, Beyer, Cook, Featherstone (Chairman), Gilman, Goodman, Mandel, Pfeiffer, and Shideman.

Second Council Meeting: (with Membership Committee) 9:00 a.m., Monday, April 10, 1961
Present: Drs. Acheson, Beyer, Cook, Featherstone, Furchgott, Goodman (presiding), Koelle, Mandel, Pfeiffer, Shideman, and Wescoe.

Third Council Meeting: 1:30 p.m., Monday, April 10, 1961
Present: Drs. Acheson, Beyer, Cook, Featherstone, Gilman (presiding), Goodman, Mandel, Pfeiffer, and Shideman.
Part time: Drs. Chen, Hodge, Koelle, Krayer, Peters, Schmidt, and Unna.

Item #I-1. Minutes of Seattle Council and Business Meetings.

The minutes of the Seattle Council and Business Meetings were approved as published on pages 17-27 of the Spring 1961 issue of "The Pharmacologist." Dr. Goodman made the motion for approval and this was seconded by Dr. Featherstone.

Item #I-2. Announcement of Meetings.

a) Coming Meetings:

	Spring	Fall
1961:	Atlantic City - Apr. 10-14	Rochester - Aug. 29-Sept. 1
1962:	Atlantic City - Apr. 16-20	Nashville (Vanderbilt Univ.)
1963:	Atlantic City - Apr. 15-19	San Francisco (Univ. of Calif.)
1964:	Chicago	Little Rock (Univ. of Arkansas)
1965:	Atlantic City	Philadelphia (Univ. of Penna.)

Item #I-2 (Cont'd).

b) 1966 Fall Meeting:

Dr. Gilman confirmed the fact that, through the courtesy of Dr. Efrain G. Pardo, an invitation had been received from Dr. Raúl Fournier Villada, Dean of the Medical School at the Universidad Nacional Autónoma de Mexico, for the Society to hold its 1966 Fall Meeting there. The invitation was enthusiastically accepted by the Council.

Item #I-3. 1961 Fall Meeting of the Society.

Dr. Harold C. Hodge met with the Council to discuss the general matters pertaining to the 1961 Fall Meeting in Rochester. It was approved that the meeting should begin on Tuesday morning, August 29, rather than the customary Monday starting date. The starting time of the meeting was delayed until Tuesday in deference to those members of the Society who were attending the Stockholm meetings and who would return too late to attend a Monday meeting. In addition, it was decided that the meeting in Rochester should be continued through Friday, September 1, with the hope that the program could be completed by Friday noon, depending upon the number of papers to be scheduled.

It was decided that the Teaching Institute should be held on Wednesday, August 30, in the Cobb Auditorium. Dr. C. A. M. Hogben had previously been selected as Chairman of the Teaching Institute, the general subject being "Gastrointestinal Pharmacology."

Also, it was decided that the Sollmann Oration should be presented at a general assembly of the Society to be held on Thursday, August 31, at 11 a.m. and that no scientific sessions would be scheduled at that hour, out of deference to the winner of the Award.

Dr. Hodge indicated that pre-registration information would be made available for mailing to the membership shortly after May 1. It was decided that the registration fee should be $12 for members and graduate students and $15 for non-members. (In a later discussion by telephone, the Council agreed that the registration fee should be $10 for members and graduate students and $12 for non-members.) There was a general discussion of facilities to accommodate both men and women, as well as families, within the university campus area and in nearby motels and hotels, etc. It was decided that the banquet tickets would be included as part of the meal tickets for those taking advantage of dormitory and meal facilities. In addition, banquet tickets would be printed for sale to those who did not make use of the university dormitories and meals. The banquet will be held on Wednesday evening, August 30. Thursday evening, August 31, was set aside for a smoker or some other appropriate entertainment to be planned by the Local Committee.

Item #I-4. Symposia at National Meetings.

It has been proposed that a larger proportion of time at the spring meeting of the Society be devoted to symposia, restricting or otherwise grouping the 10-minute papers in such a manner as to conflict as little as possible with the symposia. Although there is real merit to increasing the number of symposia, it was decided to place with the Program Committee the responsibility for bringing specific recommendations along these lines to the Council. One of the real problems at the spring meetings is the large number of rooms required for the scientific sessions; thus, space becomes a limiting factor in any additions to the present programming of the Pharmacology sessions.

Item #I-5. Proposed Amendments to the Constitution.

a) Article I. Name:

This article was read and discussed. No action was required.

b) Article IV. Officers:

This article was read and discussed. The intent and operation was considered carefully. No action was required by Council.

Both of these articles required action by the membership of the Society at its business meeting, a 4/5 vote in favor being necessary to carry these amendments.

Item #I-6. Proposed Change in Date for Installation of Society Officers.

One of the members of Council, Dr. Goodman, had suggested that it might be more efficient to install officers of the Society at the end of the second business meeting of the spring session, so that the newly elected officers might assume immediately thereafter their duties and responsibilities. The general matter of the time at which officers assume their duties is a matter of concern to the Federation at large and to the fiscal year presently employed by our Society. It was decided by Council to leave the date for the assumption of duties by the officers at July 1, as has obtained for the past several years. It was noted, however, that the American Society of Biological Chemists was similarly considering the installation of their new officers as a last item of business during the spring session.

Item #I-7. Treasurer's Report.

The Treasurer, Dr. Shideman, made a formal report of the financial affairs of the Society and called particular attention to the recommendations of the auditors with respect to putting the affairs of the Society on a more appropriate accounting basis. The suggestions of the auditors, as represented in

Item #I-7 (Cont'd).

the following statement from Ronald Mattox and Associates, dated 3-29-61, were accepted for further consideration by the Finance Committee and by the Council:

"In connection with our audit, you have asked that we make recommendations on system changes and other matters. Our comments follow:

"1. It appears that one of the problems of the treasurer is the allocation of expenditures and interest income, etc., between the various funds. We recommend that a statement of policy be adopted by the Council so that the treasurer has a basis on which to allocate these items.

"2. Your society records are currently kept on a single entry basis. We recommend installation of a complete double entry set of books for the treasurer's account. This would consist of (1) a cash disbursements journal, (2) a cash receipts journal, (3) a general journal and (4) a general ledger.

(1) Cash disbursements journal - All checks would be entered in the cash disbursements journal and extended to the various expense classifications in the appropriate fund.

(2) Cash receipts journal - The detail of deposits could be typed on the deposit slip and deposit slip totals entered in the cash receipts journal and allocated to the correct classification within each fund. It may be advantageous to make separate deposits for membership dues, Corporate Associate dues and miscellaneous receipts.

(3) General journal - The general journal would be used for recording other than cash transactions and for correcting entries.

(4) General ledger - The various journals could be totaled and posted to the general ledger monthly or quarterly.

"3. We recommend that payments to the various operating expense funds such as the editor's expense fund, Beaumont House account, etc., be made on an imprest basis and the controller of each fund account to the treasurer for all expenditures. At the time of the accounting the actual expenditures would be recorded so that the treasurer's books would show as an asset the unexpended balance in each of the various funds.

Item #I-7. (Cont'd).

"4. At the present time payments to editors, associates and secretarial help are not being reported for any payroll tax purposes. We believe payments to the editors and associate editors should be reported to the Internal Revenue Service on information returns. Also payments to the treasurer's secretary and the editor's secretary should be reported on Forms W-2 each year. A non-profit organization which is exempt from federal income taxes has the option of covering or not covering employees by social security."

Item #I-8. Report on Corporate Associates.

Dr. Gilman gave a general report on the response of the various companies to the Corporate Associate program of the Society. He announced that the receipts from the Corporate Associates were essentially the same as for 1960. An up-to-date list of Corporate Associates is published in the Fall 1961 issue of "The Pharmacologist."

Item #I-9. Ad Hoc Committee on Trust Funds.

Whereas such a committee has been discussed from time to time, Dr. Gilman indicated that these thoughts and plans had not yet been formalized.

Item #I-10. Duties and Assignments of the Treasurer and Treasurer-elect.

With the appointment of an Executive Officer of the Society to take over the managerial functions of the offices both of Secretary and Treasurer, the responsibilities of especially the Treasurer required further consideration.

It was recommended and approved that, with the retirement of the present Chairman of the Committee on Financial Resources and Budget, the Treasurer of the Society would assume the position of Chairman of this Committee, renamed the "Finance Committee" of the Society. In this position, he would have the responsibility for setting up for approval the annual budget for the Society and would have access to the records and financial affairs of the Society generally. It was also approved that the Treasurer-elect should become a member of the Finance Committee, so that he might perpetuate the function of the Chairman of that Committee at such time as he assumes the duties of Treasurer.

It was directed that the Treasurer, in his role as Chairman of the Finance Committee, should report on the financial affairs of the Society to the Council and to the membership of the Society at the time of its spring and fall meetings.

Item #I-11. Financing of New Building at Beaumont House.

Dr. Pfeiffer presented a general report on the plans for a much-needed new building at Beaumont House. A part of the financing of the new building under present consideration included increasing the Federation dues from $4 to $6 and increasing the subscription to "Federation Proceedings" from $8 to $12. This could be done without an increase in Society dues and assessment. It was anticipated that the registration fee for the spring Federation meeting would be increased to $15. The allocation of space and the over-all floor plan for the building were discussed.

Item #I-12. Working Arrangements for Dr. Cook and Dr. Mandel.

There was a discussion of work loads and responsibilities for Dr. Mandel (Secretary of the Society after July 1, 1961) and Dr. Cook (Executive Officer) during the interim period of July 1 to October 1, 1961, at which time Dr. Cook is to assume his responsibilities as Executive Officer of the Society. The arrangements were of a temporary nature.

Item #I-13. Committee Appointments and Society Representatives.

a) Committee Appointments:

The following new appointments to the several committees, recommended by the President and President-elect, were approved by the Council:

Finance Committee
Frederick E. Shideman - Chairman
Robert M. Featherstone
Treasurer-elect (Note: James A. Bain was elected to this office.)

Committee on Educational Affairs
Louis S. Goodman
Julius B. Kahn, Jr.

Committee on Professional Affairs and Public Relations
Carl Dragstedt
Ellsworth B. Cook

Program Committee
Donald J. Jenden (Note: Dr. Jenden could not accept this appointment; subsequently, Henry H. Swain was appointed by Dr. Gilman.)

Item #I-13 (Cont'd).

b) Board of Publications Trustees:

Dr. Karl H. Beyer and Dr. Lawrence Peters were appointed to the Board of Publications Trustees, to fill the two vacancies created by the expiration of the term of office of Dr. Louis S. Goodman and by the resignation of Dr. Maurice H. Seevers. (These appointments are subject to the approval of the membership at its business meeting.) Dr. Neil C. Moran will replace Dr. Lawrence Peters on the Board as Editor of "The Journal."

c) Representative to the International Union of Physiological Sciences:

Dr. Carl F. Schmidt was reappointed Society representative to the International Union of Physiological Sciences.

d) Dr. Gilman appointed Dr. Featherstone to act for him at the meeting of the Federation Board on Sunday, April 9, at 1:30 p.m.

e) The Council approved the delegation of authority as an officer of the Society to Dr. Karl H. Beyer to continue until the arrangements for the charter flights to the First International Pharmacological Meeting be completed.

Item #I-14. Abel Award.

A letter, dated 3/22/61, from Dr. K. K. Chen to the Secretary of the Society was read, confirming the renewal by Eli Lilly and Company of the John J. Abel Prize in Pharmacology for a 3-year period.

Item #I-15. Meeting of the Torald Sollmann Award Committee.

The First Council Meeting was adjourned, so that the meeting of the Award Committee (Council of the Society) to select the recipient of the first Torald Sollmann Award in Pharmacology could be convened by its Chairman, Dr. Robert M. Featherstone (Senior Councilor).

Previously, copies of the list of recommended candidates for this Award, together with their qualifications, had been circulated to all members of the Committee. The Committee elected one from the list of distinguished scientists, the name of whom was to be withheld until the time of the Sollmann Oration, to be given at the 1961 Fall Meeting of the Society in Rochester, on Thursday, August 30, at 11 a.m. It was decided that the Chairman of the Award Committee would introduce the recipient of the Award, following which the recipient would present the Sollmann Oration.

Item #II-1. Discussion of Applications with Membership Committee.

The qualifications of the 97 candidates for membership in the Society were considered carefully by the Council in discussion with Drs. George B. Koelle, W. Clarke Wescoe and Robert F. Furchgott, of the Membership Committee. From these candidates, a list of 60 proposed new members was drawn up for presentation to the Society at its first business meeting. Of those not accepted, 29 were deferred, 5 were rejected and 3 were withdrawn.

In the deliberation on the basis for selection of honorary members, it developed that there was a substantial lack of unanimity as to what should constitute the policy on this matter. Consequently, action on matters having to do with honorary membership was deferred for further consideration by the Membership Committee and for recommendation to Council.

Item #III-1. Report of the Program Committee.

Dr. Peter B. Dews, as Chairman of the Program Committee, reported on the following plans or considerations of his Committee:

He indicated that the workshop sessions at the fall meetings were well received and should be continued. This was approved by Council.

The matter of 1/2-hour introductory surveys by chairmen of selected scientific sessions was generally discussed. It was decided that such introductions were particularly worthwhile where there was a substantial homogenity of the several papers making up a session. It would be under these circumstances that a chairman would be invited to introduce the session in this manner.

Dr. Dews indicated that his Committee had considered seriously the matter of grouping of papers within sessions in such a manner as to permit a greater continuity of interests within individual sessions. It was proposed that at the fall meeting the sessions would be programmed in such a manner as to have a run of five papers of similar nature, a 15-minute break, and then five or six additional papers of essentially the same nature. This was recommended as an experiment, in order to see whether or not the idea had merit. This would permit an easier move of the membership from one session to another and an easier means for discussing individual papers during the 15-minute break. This experiment was approved by Council.

It was decided that, after the Executive Officer assumes his duties, the Program Committee would meet with him and the Secretary of the Society at Beaumont House to put the program for the scientific sessions together. It was also decided, in agreement with the Committee on Educational Affairs, that the Program Committee would take over the responsibilities for programming the Teaching Institute at the fall meetings (see Item #III-7 of these minutes).

It was suggested that there be more symposia at the fall meetings, and that these were not to conflict with the 10-minute papers (see Item #I-4 of these minutes).

Item #III-1 (Cont'd).

The Program Committee recommended that members of the Society should have the prerogative of presenting demonstrations at the fall sessions. Since no mechanism was set up for this at the time, the recommendation was taken under advisement.

Dr. Dews recommended that the Ad Hoc Committee set up to establish the Neuropharmacology Symposia as intersociety sessions for the spring meetings be disbanded. This Committee had been working for several years in collaboration with the American Physiological Society and had served its purpose.

Item #III-2. Report of the Chairman of the Board of Publications Trustees.

Dr. Otto Krayer indicated that Dr. Karl H. Beyer and Dr. Lawrence Peters were to be presented to the Society during the business meeting for approval as new appointees to the Board of Publications Trustees. The full report of the Chairman of the Board is published in the Fall 1961 issue of "The Pharmacologist."

Item #III-3. Report of the Editor of the "Journal of Pharmacology and Experimental Therapeutics."

Dr. Lawrence Peters reported on the editorial activities relating to the "Journal of Pharmacology and Experimental Therapeutics" during the year 1960. His full report is published in the Fall 1961 issue of "The Pharmacologist."

He indicated that Dr. Neil C. Moran would assume the responsibilities of Editor of "The Journal" on October 1, 1961, and that Dr. Marion DeV. Cotten had taken over as Assistant Editor in June 1960.

Item #III-4. Report of the Editor of "Pharmacological Reviews."

Dr. George B. Koelle presented his report on the editorial activities of "Pharmacological Reviews" during 1960. This is published in the Fall 1961 issue of "The Pharmacologist."

Item #III-5. Report of the Committee on Financial Resources and Budget.

Dr. K. K. Chen, Chairman of the Committee on Financial Resources and Budget, presented to the Council a report on the itemized budget estimate for 1961-62, which was arrived at by the Committee at a meeting the evening before. After the addition of two small entries by Dr. Krayer, Chairman of the Board of Publications Trustees, the budget was approved and adopted as proposed, and included in the Committee's detailed report. This completed the Society's plan for operations at Beaumont House.

Item #III-6. Report of the Committee on Professional Affairs and Public Relations.

Dr. Harold C. Hodge, Chairman of the Committee on Professional Affairs and Public Relations, presented to the Council his report on the activities of that Committee during 1960-61. His full report is published in the Fall 1961 issue of "The Pharmacologist."

In the discussion of this report, two resolutions were sent forward by the Council for approval by the Society at its business meeting. The first one concerned the loyalty oath affidavit of the National Defense Education Act. The second concerned courses for doctors in practice. In the latter connection, Dr. Goodman had suggested that we should endorse the suggestion made by Drs. Darley and Cain that a National Academy of Continuing Medical Education be established and that we assist in this effort. The Council instructed Drs. Hodge and Goodman to draw up a positive statement for presentation to the membership of the Society for approval at its business meeting.

Item #III-7. Report of the Committee on Educational Affairs.

Dr. Klaus R. Unna, Chairman of the Committee on Educational Affairs, reported on the activities of his Committee. He presented plans for the distribution of the second edition of the brochure, "A Career in Pharmacology," to science teachers, libraries and vocational guidance teachers at high schools and colleges during 1961. Individual inquiries and requests for the brochure have steadily increased to an average of between 300 and 500 per month.

The graduate training grant from the National Institutes of Health in support of the activities of the Committee on Educational Affairs covered in its first year the period from January 1, 1961 through June 30, 1961. A second year's support is committed for the period from July 1, 1961 through June 30, 1962. A progress report and an application for a new grant were extensively discussed.

Preparations for a Teaching Institute in 1962 at Nashville are under way. In consultation with the Program Committee, it was agreed that the responsibilities for organizing the Teaching Institutes after the 1962 Fall Meeting would devolve on the Program Committee. The Council concurred with this proposal.

Item #III-8. Report on the First International Pharmacological Meeting in Stockholm.

Dr. Carl F. Schmidt stated that preparations for the First International Pharmacological Meeting in Stockholm on August 22-25 are well along. About 1500 people have enrolled as members of the Meeting, and the prospects are for 1800-2000 by the time August 22 arrives. Dr. Uvnäs and his colleagues

Item #III-8 (Cont'd).

recently visited Leningrad and Moscow and succeeded in enlisting the hearty cooperation of the Russians, who previously had held back because of insufficient information about the nature and objectives of the Meeting. The Section on Pharmacology of the IUPS may have an opportunity within the next year of becoming an independent Associate Union in ICSU. Dr. Schmidt asked the members of the Council for an expression of their feelings on this matter. Those who responded spoke in favor of an independent International Union of Pharmacologists as soon as suitable arrangements can be made.

Item #III-9. Necrology Record.

John A. Eyster - March 16, 1960
Philip Hitchcock - April 17, 1960
James C. Rice - May 9, 1960
Henry M. Lee - June 12, 1960
Henry W. Newman - July, 1960
Edward E. Swanson - August 14, 1960
Paul K. Smith - October 6, 1960
Harold A. Shoemaker - November 2, 1960
E. A. Rovenstine - November 9, 1960
Victor P. Seeberg - December 28, 1960
Worth Hale - January 15, 1961

Item #III-10. Retired Members.

Hamilton H. Anderson
G. S. Eadie
Owen S. Gibbs
Eugene L. Jackson
Isaac Neuwirth
R. A. Waud

Item #III-11. Riker Fellowship.

After discussion of the applications for the 1961-62 Riker International Fellowship in Pharmacology, the Council selected Dr. Rose Dagirmanjian as the Society's nominee for the renewal of her Fellowship for study with Dr. Marthe Vogt at Babraham, England.

MINUTES OF BUSINESS MEETINGS
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Borton Hall, Dennis Hotel
Atlantic City, New Jersey

First Business Meeting: 4:30 p.m., Tuesday, April 11, 1961
(308 members present)

Second Business Meeting: 4:30 p.m., Thursday, April 13, 1961
(185 members present)

Item #1. Minutes of the Seattle Business Meetings.

The minutes of the Seattle Business Meetings were approved as published on pages 17-20 of the Spring 1961 issue of "The Pharmacologist."

Item #2. Proposed Amendments to the Constitution.

a) Article IV. Officers:

The proposed amendment to the Constitution pertaining to the officers of the Society was read as follows:

" SECTION 2. The President-Elect, either the Secretary-Elect or the Treasurer-Elect, and one other Councilor shall be elected at each annual meeting and shall become members of the Council on the following July 1.

" SECTION 3. The President-Elect shall become President after one year as President-Elect, except as otherwise provided in Section 6A. He shall continue to serve as President until two years after having assumed office as President-Elect, at which time he shall become Past-President for one year.

" SECTION 6A. If the office of President, Secretary or Treasurer becomes vacant, the corresponding officer-elect shall succeed to office.

" SECTION 6B. Vacancies on the Council or elected committees shall be filled in one of two ways, as determined by the Council: Candidates nominated by the Nominating Committee either may be elected at the next meeting of the Society or in the interim by majority vote of the Council.

" SECTION 6C. A nominee selected by the Council to maintain its number, when vacancy is created in the office of either the Past-President, President, President-Elect or Councilor, shall be designated a Councilor. He shall serve until the vacancy is filled by election at the next meeting of the Society.

Item #2. a) (Cont'd).

" The Council, in accordance with Section 6B may designate a Secretary, Secretary-Elect, Treasurer or Treasurer-Elect to serve for the unexpired term of the vacated office. A Secretary-Elect or Treasurer-Elect so chosen shall succeed to the corresponding office."

There was no discussion of the article from the floor. The proposed amendment to Article IV was put to a vote and the change was AFFIRMED. The vote was 285 in favor, 2 opposed, and 5 abstaining.

b) Article I. Name:

The proposed amendment to Article I, pertaining to the name of the Society, was read as follows:

" The name of this organization is the AMERICAN SOCIETY FOR PHARMACOLOGY, INCORPORATED."

This article was discussed from a historical standpoint by Dr. E. M. K. Geiling, who contradicted an impression previously presented to the Society questioning whether or not Dr. Abel had included "and Experimental Therapeutics" in the name of the Society in his recommendation for reasons of expediency. Dr. Geiling indicated that, from evidence available to him, Dr. Abel felt that the inclusion of "and Experimental Therapeutics" in the title was most appropriate.

Dr. Avram Goldstein felt that, whereas previously he had been in favor of the change in name of the Society, he would wish to respect the desires of a substantial minority in the matter.

Other aspects of the change in name of the Society were presented by Dr. Albert Sjoerdsma and by Dr. Gordon Alles.

Dr. Goodman moved that the issue be put to a vote, and this was seconded. The vote on the amendment was 141 in favor, 144 opposed, with 7 members abstaining. Thus, the proposed amendment to Article I of the Constitution was DEFEATED.

Item #3. Election of Officers for 1961-62.

The slate of candidates for office, as published in the Spring 1961 issue of "The Pharmacologist," was presented to the membership by the Nominating Committee as follows: for President-elect - Oliver H. Lowry, H. B. van Dyke; for Treasurer-elect - James A. Bain, Jurg A. Schneider; for Councilor - Lawrence Peters, Klaus R. W. Unna; for Membership Committee - Herbert L. Borison, John J. Burns.

Item #3 (Cont'd).

Nominations of 10 candidates for the Nominating Committee were made from the floor as follows: T. K. Adler, W. M. Booker, K. K. Chen, N. A. David, K. F. Killam, Jr., T. O. King, P. S. Larson, K. S. Lee, A. S. Marrazzi, and D. P. Rall.

Ballots were cast. The vote for the office of President-elect was tied on the first ballot taken at the first business meeting on April 11. A second ballot was taken during the second business meeting on April 13, and Dr. H. B. van Dyke was elected to the position of President-elect. As a result of the elections, the officers of the Society for 1961-62 are as follows:

President:	Carl C. Pfeiffer	Past-president:	Alfred Gilman
President-elect:	H. B. van Dyke	Councilors:	
Secretary:	H. George Mandel		Walter F. Riker, Jr. (1962)
Treasurer:	Frederick E. Shideman		George H. Acheson (1963)
Treasurer-elect:	James A. Bain		Lawrence Peters (1964)

Dr. John J. Burns was elected to the Membership Committee for a three-year term. The members of the Nominating Committee for 1961-62 are: K. K. Chen (Chairman), Walter M. Booker, Keith F. Killam, Jr., Paul S. Larson, and Amedeo S. Marrazzi.

Item #4. Report of the Membership Committee -- Election of New Members.

Dr. George B. Koelle, Chairman of the Membership Committee, presented the list of 60 candidates recommended for membership in the Society, following the deliberations of the Membership Committee in combined session with the Council. The names of these candidates for membership were formally "posted" during the first business meeting.

As a result of the secret vote cast by the membership of the Society during the second business meeting, all 60 candidates were elected to membership in the Society. This brings the total membership of the Society to 961.

Item #5. Appointments to the Board of Publications Trustees.

Dr. Gilman presented to the membership of the Society the names of Dr. Lawrence Peters and Dr. Karl H. Beyer as new appointments to the Board of Publications Trustees. The appointments were ratified by those in attendance at the first business meeting.

Item #6. Introduction of Dr. Ellsworth B. Cook, Executive Officer.

Dr. Ellsworth B. Cook was introduced to the Society by Dr. Gilman. Dr. Gilman reviewed the basis for the selection of the Executive Officer, the action of the Search Committee (composed of Drs. Krayer, Goodman and Gilman), and, in turn, the qualifications of Dr. Cook for this office.

Item #7. Announcement of Coming Meetings.

a) Fall Meetings of A.S.P.E.T.:

1961: Rochester, Aug. 29-Sept. 1
1962: Nashville (Vanderbilt)
1963: San Francisco (Univ. of Calif.)
1964: Little Rock (Univ. of Arkansas)
1965: Philadelphia (Univ. of Penna.)

The official invitation to hold the 1966 Fall Meeting of the Society at the Universidad Nacional Autónoma de Mexico, Mexico City, was confirmed.

b) Federation Meetings:

1962: Atlantic City, Apr. 16-20
1963: Atlantic City, Apr. 15-19
1964: Chicago
1965: Atlantic City

c) Canadian Federation of Biological Societies, Guelph, Ontario, May 31-June 2, 1961.

d) Third Inter-American Conference on Occupational Medicine and Toxicology, Coral Gables, Fla., Aug. 6-10, 1961.

e) First International Pharmacological Meeting, Stockholm, Sweden, Aug. 22-25, 1961.

Dr. Carl F. Schmidt reviewed briefly the plans for the First International Pharmacological Meeting in Stockholm, indicating that, even though the deadline had passed, abstracts of papers for presentation at the meeting were still being accepted.

Dr. Karl H. Beyer then reviewed the arrangements for charter flight service to the Stockholm meetings. He indicated that there were still a few openings on the flights and that the charter had been rewritten to include "delegates" to the meetings other than Society members.

f) XXII International Physiological Congress, Leiden, Netherlands, Sept. 11-17, 1962.

Item #7 (Cont'd).

g) Status Report on 1961 Fall Meeting:

Dr. Harold C. Hodge made a general statement regarding the arrangements for the 1961 Fall Meeting in Rochester. He indicated that plans were well under way and that complete information would be mailed to the membership on or about May 1.

In the second business meeting, it was pointed out by Dr. Gilman that the abstracts for this meeting should be in the hands of the Secretary, Dr. Karl H. Beyer, by JUNE 16, 1961.

Item #8. Torald Sollmann Award in Pharmacology.

Dr. Gilman announced that the recipient of the Torald Sollmann Award had been elected by the members of Council, acting as the Award Committee under the chairmanship of the senior councilor, Dr. Robert M. Featherstone. He announced that the Sollmann Oration would be given at a convocation of the Society on Thursday, August 31, 1961, at 11 a.m. in Rochester.

Item #9. Committee and Officer's Reports.

a) Treasurer's Report:

Dr. Frederick E. Shideman reported on the favorable financial status of the Society, presenting figures as follows. At the beginning of the fiscal year on April 1, 1960, the total assets of the Society amounted to $68,888.50. During the year, income from dues, publications, meetings, and interest on bonds and savings account totalled $78,387.85. The total disbursements during this period were $42,128.03, providing a net fund balance as of April 1, 1961 of $105,148.32. However, there were cash balances existing at this time in the Secretary's, Editor of the Journal's, Editor of Pharmacological Reviews', and Beaumont House Funds in the amount of $16,273.08, which, when added to the net fund balance of $105,148.32, is $121,421.40, the assets of the Society as of April 1, 1961. The Treasurer's Report, as presented to the Council and officially placed on file, has been audited as of March 31, 1961.

b) Committee on Financial Resources and Budget:

During the first business meeting on April 11, Dr. K. K. Chen presented his report on the activities of the Committee on Financial Resources and Budget, as follows: "On behalf of the Committee on Financial Resources and Budget, I wish to report that our Committee together with several Council members spent the whole evening last Sunday on the preparation of a budget estimate covering the fiscal year from April 1, 1961 to March 31, 1962. This was approved by the Council yesterday afternoon. Our plans are completed for

Item #9. b) (Cont'd).

the full operation of our Society and Journal activities at Beaumont House in Bethesda, Maryland. This is a particular pleasure to me, because Beaumont House was purchased when I was Chairman of the Federation Board. It is a beautiful site, and our members should visit the headquarters when they are in Washington, D.C. or Bethesda.

"The members of our Committee and Council examined the financial position of the Society very carefully. We have a substantial reserve in the treasury. Our regular annual income consists of membership dues and journal proceeds. The Corporate Associate program is a vital supplement to our receipts. Through the efforts of President Gilman and Past-Presidents Krayer and Goodman, and through the efforts of our own members working in drug industry who successfully convinced their managements to give continuous support, the financial structure of our Society is secure for the next 5 to 10 years. The members of the Committee and Council discussed other resources, including tax-deductible contributions of our members who are financially more fortunately situated, to insure perpetuation of the activities of our Society."

A standing vote of thanks was extended by the membership to Dr. K. K. Chen for all of his efforts in behalf of the Society, as he retires as Chairman of the Committee on Financial Resources and Budget.

c) Committee on Educational Affairs:

Dr. Klaus R. Unna, Chairman of the Committee on Educational Affairs, reported on the activities of his Committee during the past year. He announced that a nation-wide distribution of the second edition of the brochure, "A Career in Pharmacology," has been started. The numbers of individual requests for the brochure and for further information which have reached Beaumont House are increasing. The inquirers receive, besides the brochure, suggestions for their undergraduate curriculum, a list of all departments offering graduate education in pharmacology and a letter advising the inquirer to contact a Department of Pharmacology near his home or college.

The Committee prepared an exhibit, "Choose a Career in Pharmacology," and presented it at the A.A.A.S. Meeting in New York City on December 27-31, 1960. Plans are made to display the exhibit at science fairs and other educational meetings.

The Survey on Graduate Education in Pharmacology has been reported in detail in the Spring 1961 issue of "The Pharmacologist," pp. 43-56.

The Teaching Institute on "Gastrointestinal Pharmacology" will be held under the chairmanship of Dr. C. A. M. Hogben at Rochester on Wednesday, August 30, 1961.

Item #9 (Cont'd).

d) Program Committee:

Dr. Peter B. Dews reported on the activities of the Program Committee during the past year. During 1960-61, the Program Committee continued its now routine functions of sorting and sequencing 10-minute paper sessions for the spring and fall meetings. Two workshop sessions were arranged at the Seattle meeting, one conducted by Drs. M. H. Seevers and E. L. Way and the other by Drs. W. F. Riker, Jr. and D. B. Taylor. The unstructured polling system used by the Program Committee to evaluate results of its activities led to the conclusion that these were successful; so it is proposed to arrange further workshops for the Rochester meeting. The Program Committee also proposes to continue to invite selected chairmen to give 30-minute introductions to 10-minute paper sessions. These invitations will be made when, during the sorting of papers, clusters of papers or relatively high degree of homogeneity emerge, and when a suitable chairman is available.

Two innovations were recommended to Council. The first is that the sessions of contributed papers be organized in groups of 5 or 6 (instead of 10 or 11 as now). Mornings and afternoons would then contain two consecutive sessions, separated by a 15-minute break. Hopefully, this would permit the papers of sessions to be more closely related to one another and might encourage people to switch sessions at break-time rather than when a quietly speaking author is explaining an involved, though crucial, point. Finally, the arrangement would allow the chairman a little more latitude in timing; he could permit a particularly vivacious discussion to continue longer in the reassuring knowledge that the simultaneous sessions would get back in phase at break- (or lunch-) time.

The second recommendation followed the suggestions of Dr. Avram Goldstein that there be more symposia-type proceedings at the national meetings. People active in particular lines of research would be invited to talk on their current activities and interests. The proceedings would not be published, and the speakers would be under no obligation to provide comprehensive background reviews. Thus, participation should not be too much of a burden. Individual sessions may or may not be grouped around a common topic. Some topics may be expected to become more or less regular features, year after year, while others would be infrequent. The symposia would not be run simultaneously with contributed paper sessions. The hope is that these types of symposia would enhance both the inspirational and educational value of the Society's meetings.

e) Board of Publications Trustees:

Dr. Otto Krayer presented his report as Chairman of the Board of Publications Trustees. This report is published in full in the Fall 1961 issue of "The Pharmacologist."

Item #9 (Cont'd).

f) Reports of Editors:

Dr. Lawrence Peters presented his report as Editor of the "Journal of Pharmacology and Experimental Therapeutics," following which Dr. George B. Koelle reported on the activities of the editorial office of "Pharmacological Reviews." These reports are recorded in the Fall 1961 issue of "The Pharmacologist." In addition, Dr. Peters announced that Dr. Neil C. Moran would assume the responsibility of Editor of "The Journal" as of October 1, 1961.

g) Committee on Professional Affairs and Public Relations:

Dr. Harold C. Hodge reported on the activities of the Committee on Professional Affairs and Public Relations during the past year. His detailed report is published in the Fall 1961 issue of "The Pharmacologist."

Two resolutions were sent forward by the Council to the Society for approval. The first, pertaining to the loyalty oath affidavit of the National Defense Education Act, was read as follows:

> "Resolved that the American Society for Pharmacology and Experimental Therapeutics condemns the loyalty oath affidavit of the National Defense Education Act because it is unnecessary and ineffective, and instructs the Secretary to inform the other societies of the Federation of its decision and to inform the general press and the editors of "Science," "Scientific American" and the "American Scientist" of this resolution."

This resolution was CARRIED by the members in attendance at the second business meeting on April 13.

The second resolution, which was concerned with courses for doctors in practice, was read as follows:

> "Resolved that the officers of the American Society for Pharmacology and Experimental Therapeutics be instructed to inform the American Medical Association through its Executive Vice-President, Dr. F. J. L. Blasingame, and the Association of American Medical Colleges through its Executive Director, Dr. Ward Darley, that the Society stands ready to assist, with particular reference to rational drug therapy, in the activities of the proposed National Academy of Continuing Medical Education, as outlined in the January issue of the "Journal of Medical Education."

This resolution was CARRIED unanimously by the members in attendance at the second business meeting on April 13.

Item #10. Federation Items of Interest to Society.

Dr. Gilman indicated that the registration for the Federation Meeting to date was 12,280. This does not represent necessarily the final registration for the meeting.

It was announced that abstracts for the 1962 Federation Meeting should be in the hands of the Executive Officer of the Society, Dr. Ellsworth B. Cook, by DECEMBER 30, 1961.

Dr. Pfeiffer reported on the following Federation items of general interest to the Society. He indicated that the cost of new construction at Beaumont House would approximate $350,000. It is expected that the funds for this expenditure would derive from such sources as an increased fee for exhibits and an increase in the registration fee for the Federation Meetings from $10 to $15, with an increase in rebate to the societies to $4 for each member registering. He indicated that subscriptions to "Federation Proceedings" for non-members would be increased from $8 to $12, and that it is planned to issue "Federation Proceedings" on a bimonthly, rather than on a quarterly, basis. Also, it is planned to issue the program for the spring meeting separately from "Federation Proceedings" and in the form of a throw-away spiral-bound pocket-size booklet, which would be more convenient for carrying.

Dr. Pfeiffer also mentioned the following antivivisection bills. The Griffiths Bill (HR 1937) and the Moulder Bill (HR 3556) have been introduced into the House of Representatives. They have been referred to the Committee on Interstate and Foreign Commerce of the House of Representatives. Hearings on these proposals have not as yet been scheduled. The Cooper Bill had not been introduced into the Senate as of the time of the Society business meeting. Dr. Pfeiffer stressed the importance of members being familiar with the contents of these bills and of their participation by writing to their Washington representatives emphasizing their attitudes and their points of view regarding these bills.

Item #11. Necrology Announcements.

The necrology announcements were read as follows:

John A. Eyster - March 16, 1960
Philip Hitchcock - April 17, 1960
James C. Rice - May 9, 1960
Henry M. Lee - June 12, 1960
Henry W. Newman - July, 1960
Edward E. Swanson - August 14, 1960
Paul K. Smith - October 6, 1960
Harold A. Shoemaker - November 2, 1960
E. A. Rovenstine - November 9, 1960
Victor P. Seeberg - December 28, 1960
Worth Hale - January 15, 1961

Item #12. New Business.

The suggestion was made from the floor that, for next year, the page numbers of Federation abstracts be included appropriately beside the title of the paper in the program. This matter has been referred to the Federation Secretaries Committee.

Item #13. Adjournment.

In closing the session, Dr. Gilman expressed his appreciation to the officers who served with him during his appointment. Dr. Otto Krayer expressed the appreciation of the Society membership to Dr. Gilman on the occasion of his last appearance as President of the Society.

Report of the Chairman of the Board of Publications Trustees

1. Journal Operations: In 1960, the Journal published three volumes. The regular page allowance of 1200 double-column pages did not accommodate the increased supply of publishable material. Hence, 200 excess pages were authorized by the Board and were paid for from regular Journal income (at about $25 per page). It was decided last year to publish four volumes of 400 pages each, starting January 1, 1961. This should take care of what appears to be a regular increase in supply of manuscripts. There is every indication that by midyear 1961 the delay between acceptance of a manuscript and appearance in print will have been reduced to about 5 months (from 9 or more).

Pharmacological Reviews continues to show its steady increase in subscriptions; with an active list of 2,259 subscribers, it has now nearly reached the subscription list of the Journal, with 2,316 subscribers. Of the 550 single-column pages authorized, 538 were utilized in 1960. The former figure appears to be a suitable page allowance per year for Reviews.

The operation of the journals during 1960 was financially successful and resulted in a profit.

2. Beaumont House Office: During 1960, there was considerable difficulty in recruiting full-time personnel to replace two staff members who moved from the Washington area. However, Miss Bates succeeded, on July 5, in finding a secretary and, on October 3, in appointing an editorial assistant, both of very good quality. The office is now well staffed and capable of handling the nonscientific editorial matters competently and efficiently. The present staff, then, consists of: Miss Eleanor Bates, Secretary of Publications; Mrs. Marguerite A. Westfall, Editorial Assistant; and Mrs. Virginia A. Burrow, Secretary. The staff was engaged not only in journal affairs. About 1/20 of its time was spent on Society affairs of various kinds.

Toward the end of 1961, the new Executive Officer, Dr. Ellsworth B. Cook, will come to Beaumont House. He will then begin working out the relationship of the editorial office to the larger framework of the Society's Beaumont House operation.

Otto Krayer, Chairman

Report of the Editor of the "Journal of Pharmacology and Experimental Therapeutics"

The following is a report of editorial activities relating to the "Journal of Pharmacology and Experimental Therapeutics," primarily for the year 1960.

The first table, presented below, concerns the disposition of manuscripts received during the calendar year 1960, the information being complete to the end of March 1961. Comparable data are presented for the three preceding years.

	1960	1959	1958	1957
Accepted for publication	162	206	139	142
Combined with others	1	1	3	1
Withdrawn by authors	2	5	4	6
Out for revision, not yet returned	47 (16%)	35 (11%)	38 (14%)	29 (12%)
Rejected	82 (28%)	81 (24.5%)	84 (31%)	73 (29%)
Total manuscripts received	294	328	268	251

The number of manuscripts submitted in 1960 is not as large as that submitted in 1959 but is greater than that submitted in any previous year.

The actual publication statistics for each calendar year from 1957 through 1960 are presented below.

	1960	1959	1958	1957
Manuscripts from 1955	0	0	0	1
Manuscripts from 1956	0	0	0	101
Manuscripts from 1957	0	3	77	75
Manuscripts from 1958	0	82	68	--
Manuscripts from 1959	133	72	--	--
Manuscripts from 1960	60	--	--	--
Total manuscripts published	193	157	145	177

The number of papers published in 1960 (193) is larger than in any previous year.

The contractual allotment of text pages for 1960 was 1200, an increase of 156 over 1959. However, in view of the increase in the number of manuscripts received during 1959 and early 1960 and the resultant backlog of accepted manuscripts accumulated by April 1, 1960, it was agreed and announced

a year ago that up to 200 additional uncontracted text pages should be purchased during 1960 at the Journal's expense. Thus, 1400 text pages were published. This did not reduce the backlog but prevented it from increasing further during a year when we were waiting for the introduction of an additional volume. A further additional 112 pages, charged to the Journal's account, were used in 1960 to publish the volume indexes by the cheaper offset process. Text pages published per volume were as follows: Volume 128, 428; Volume 129, 476; Volume 130, 496. The average number of pages per manuscript was 7.25, as compared to 6.8 in 1959 and 6.6 in 1958.

The following table illustrates the monthly receipt of manuscripts during 1960.

Month	No. Received	Month	No. Received
January	30	July	20
February	24	August	30
March	26	September	24
April	18	October	19
May	31	November	29
June	21	December	22

Total: 294 manuscripts

Average (1960): 24.5 ms./mon.
Average (1959): 27.3 ms./mon.
Average (previous years): 22. ms./mon.

The average of 24.5 per month is below the average for 1959 but above that for three previous years. Eighty new manuscripts have been received during the first three months of 1961 (26.7 per month).

The introduction of an additional volume in 1961 results in a total annual page allotment of 1600 pages, or 200 pages more than were used in 1960. The statistics presented concerning the number of manuscripts received in 1960 and early 1961 indicate that this allotment is realistic, that it will permit reduction of our backlog of accepted, unpublished manuscripts and will reduce the lag period in publication. It has taken some time for this last to make itself felt, but one-half of the papers appearing in the May issue of 1961 will be published 5 to 5-1/2 months after receipt, while papers published in 1960 carried a lag of 7 to 9 months. A further reduction, to a lag as short as 4 months is anticipated.

Actual printing delays have remained minimal and the Journal is consistently reaching subscribers near the end of the month named on the cover.

In June of 1960, Dr. Marion DeV. Cotten became Assistant Editor of the Journal to replace Dr. Neil C. Moran, who served as Acting Editor for three months during my absence and who upon my return began a year's sabbatical leave. Dr. Moran will assume the Editorship upon his return from Europe on October 1, 1961, at which time my own Editorship will terminate. The Office

of the Secretary of Publications, under the very able direction of Miss Eleanor Bates, has continued to function in a highly effective manner in its services to the "Journal." The Editors for Specific Fields and the members of the Editorial Board have continued to give freely and unselfishly of their time in their valuable volunteer work for the Society. Their high level of conscientious performance, so essential to the "Journal," has continued to be most gratifying. We have also continued to enjoy the assistance of numerous consultants who have been called upon from time to time to review manuscripts in their particular fields of research interest and achievement. To all of the individuals mentioned, I should like to express my sincere thanks for their unstinting help and service. My gratitude to them, to the Board of Publications Trustees and to the members of the Society warrants particular expression in this official annual report, which is my last as the Journal's Editor.

Lawrence Peters, Editor

Report of the Chairman of the Editorial Board of "Pharmacological Reviews" for 1960-61

"Pharmacological Reviews" published 538 pages in Volume 12, 1960, leaving a balance of 12 pages credited to 1961. On the basis of material on hand and commitments, the Editorial Board has every expectation of utilizing these additional pages in addition to the 550 regularly allotted for the publication of review articles of high calibre and wide and varied scope in Volume 13, 1961.

New appointments to the Editorial Board in 1960 to replace members whose terms expired were Dr. A. S. V. Burgen of McGill University (replacing Dr. Nickerson) and Dr. Seymour S. Kety, then of the National Institutes of Health, now at Johns Hopkins University (replacing Dr. Krayer).

New appointments to the Editorial Advisory Board replacing retiring members include Dr. I. R. Innes of Winnipeg and Dr. J. Mardones of Santiago.

Dr. Robert L. Volle, of the University of Pennsylvania, was appointed to the new position of Assistant to the Editor.

George B. Koelle, Chairman

Report of the Chairman of the Committee on Professional Affairs and Public Relations

The Committee on Professional Affairs and Public Relations met at 2 p.m. on Sunday, April 9, 1961, in Room #3 of the Dennis Hotel in Atlantic City. Drs. E. Bueding, G. E. Farrar, N. J. Giarman, H. C. Hodge (Chairman), F. S. Philips and M. L. Tainter were present.

1. The Committee recommended to the Council that in the future the Program Committee be given formally the responsibility for the selection of newsworthy abstracts since, when they handle the abstracts at the time the scientific program is assembled, they have an excellent chance to pick out those with unusual interest.

2. The Committee approved four resolutions for submission to Council, as follows:

a) A resolution on drafting graduate students: "The American Society for Pharmacology and Experimental Therapeutics draws attention to the critical shortage of trained pharmacologists. These trained scientists occupy a key position in our national effort; theirs are such tasks as the training of physicians, the development of new drugs and the protection of health through toxicological research. Interrupting the training of young scientists about to enter the field of pharmacology is intolerably wasteful unless they are assigned immediately to duties in which their professional skills are utilized and further developed. The Secretary is directed to transmit this resolution to the appropriate federal authorities."

b) A resolution concerning the loyalty oath affidavit of the National Defense Education Act: "Resolved that the American Society for Pharmacology and Experimental Therapeutics condemns the loyalty oath affidavit of the National Defense Education Act because it is unnecessary and ineffective, and instructs the Secretary to inform the other societies of the Federation of its decision and to inform the general press and the editors of "Science," "Scientific American" and "The American Scientist" of this resolution." (This resolution was approved by Council for presentation to the Society during its business meeting.)

c) A resolution in opposition to the Cooper-Griffiths Bill: "Resolved that the American Society for Pharmacology and Experimental Therapeutics affirms its opposition to the Cooper-Griffiths Bill on the grounds that it is poorly conceived, poorly constructed and will not fulfill its objectives. The Secretary is instructed to convey the opposition of this Society to appropriate legislators. Each Society member is requested to declare his opinion of this measure to his representatives in Congress. The Secretary is instructed to distribute to the members a critical summary of the Cooper Bill prepared by the Committee on Professional Affairs when the Cooper Bill is introduced."

d) A resolution on continuing courses for doctors in practice. The Committee felt that medical schools should prepare courses for doctors in practice designed to present information about drugs and that the Society has a responsibility to develop and promote an active program in collaboration with the clinical teachers. (This resolution was approved by Council in a revised form for presentation to the Society during its business meeting.)

Harold C. Hodge, Chairman

Report of the Representative to the Division of Medical Sciences, National Research Council

The Annual Meeting of the National Research Council was held in the National Academy of Sciences Building, Washington, D. C., on March 9-11, 1961.

The plenary sessions were presided over by President Bronk. These sessions considered the following subjects: a) instrumentation and its scientific significance; b) the Mohole and engineering problems; and c) reports from the various sections.

Other simultaneous plenary sessions considered: a) the role of mathematics in other sciences; b) what the public should understand about science; and c) problems created by the rapid growth of science.

The Division of Medical Sciences met on Friday, March 10, 1961, at 1:30 p.m. and held a divisional dinner that evening. The following definitive actions were taken by the section:

1. The following society was admitted for membership on the Council: Society for Investigative Dermatology. The following societies were declined membership on the basis that they are already adequately represented: American Academy of Dermatology and Syphilology; Radiation Research Society; and the Society for Experimental Biology and Medicine.

2. The section took action to convoke an autumn meeting in addition to the annual spring meeting.

3. The following addresses were heard by the section and contributed greatly to its interest: a) The Medical Interests of the International Cooperation Administration; b) The Interests of the Division of International Health, U. S. Public Health Service; and c) The National Library of Medicine and the Problems of Communication in the Medical Sciences. The difficult problem of

scientific communication was discussed. The publication explosion that is paralleling the population explosion was also considered. No definitive solutions were forthcoming.

John C. Krantz, Jr.

DR. R. KEITH CANNAN: PRINCIPAL SPEAKER AT THE SPRING 1961 PHARMACOLOGY SOCIETY DINNER

In the following pages there is reproduced the text of Dr. Cannan's address given at the Society dinner during the 1961 Federation Meeting in Atlantic City. The talk was so unusual in content and in the way it was delivered that those privileged to hear Dr. Cannan will long remember it pleasantly. Dr. Cannan was prevailed upon to make it more generally available to the Society by publication in "The Pharmacologist." Although the reader will necessarily miss the fine manner of its presentation, he is bound to share the delight with which it was received by those so fortunate as to have been present on that occasion.

SACRED AND PROFANE SCIENCE

An unusual event enlivened the proceedings of the Annual Banquet of the Academy at the Hotel Dennis, Atlantic City, on April 12.

The speaker was R. Keith Cannan, Chairman of the Division of Medical Sciences, National Academy of Sciences - National Research Council. He surprised and intrigued his audience by declaring that he was abandoning the advertised subject of his address in order to bring to the attention of the members of the Society a literary find "second only in historical importance to the uncovering of the Dead Sea Scrolls."

Dr. Cannan affirmed that, while rummaging in the archives of the Academy recently, he discovered a musty volume embellished on its cover with an engraving of a pestle and mortar. Since the contents were written in cipher the volume was referred to CIA whose experts decoded it with little ado. It then became manifest that the document was none other than the missing volume of the diary of Samuel Pepys. Since it covered the period in which Mr. Pepys was secretary to the Royal Society of Apothecaries, Dr. Cannan said that he felt that the members of our society should be privileged to learn something of the contents of the volume before it was released to the literary world at large.

Thereupon, Dr. Cannan proceeded to read extracts from the diary.

Peeps into a Diary.

Dec. 31, 1660

By candlelight did abide late on my accounts. Praise be to God, at the end of the year do find myself the richer by £40 than I did know. This does give me real content, as it is also much to my taste that I do begin the New Year in my new office as clerk to the Royal Society of Apothecaries. Though this do promise me nothing of pay, by God's grace will bring me in company of men of quality. The more, that I may find one among the members that shall give me a cure for my stone - the which I sorely need.

Jan. 1, 1661

Up at six. It being a brave day, took horse to town, where did meet the President of the Society, Alfred, Lord Gilman. Knowing him to be overly given to the study of the sick and the ill-humored, I feared me to discover him a sober and a melancholy man. So was I out of countenance to find him a pretty gentleman, excellent humored and most knowing.

My Lord did forthwith instruct me in my office; that I handle the correspondence with due haste but with all decorum, that letters to members of the Editorial Board be writ in Latin but to all others in the vulgar; that I make due plans for the meetings of councils, boards, and committees and for the annual assembly to be held in April; that I execute the elections

of officers and members, and that I take mindful note to collect the dues of members before April 15, this being the day for the paying of taxes to the King.

My Lord, right merrily, informed me that these divers duties be all for my execution, there being no others for the doing of them. The which I found a hard saying. It did discomfort me that I should promise all manner of service I knew ill to perform. The more, knowing sundry among the Council to be men obdurate of opinion, and I hasty of temper, I was much feared I would often offend.

Whereupon, My Lord, did tutor me most cunningly on such matters:

The First - That my communications be writ with such circumlocution that those to whom they be addressed may freely interpret them in such sense as best pleases them;

The Second - That, when a question does exceed my ingenuity to resolve it, I do appoint a committee. So, in natural course, the matter will be long settled and forgot before the committee hath contrived any opinion on it;

The Third - The matter of election of members should be brought to simple issue by devising some arithmetic means for the ordering of it. To wit, My Lord suggested a formula as follows: that the reprints submitted shall be weighed and, then shall be multiplied by the number of children with which the applicant is blessed and the whole shall be divided by his age. If the final number be greater than one the applicant shall be forthwith declared worthy of membership. The merit of this scoring, My Lord affirmed, was that it would restrict membership to those of sober age and would eliminate all bachelors who, to his mind, were persons of unorthodox opinion and unseemly in public behaviour.

Foremost of all, My Lord did commend to me a considerable book writ by him and by another apothecary, a Goodman and true, assuring me it clearly proved and demonstrated all questions I might have, with all known objections solidly and fully answered. He, making no offer of a gift of it, I did foresee that such investment would put me down some several pounds. I know not whether the buying or the reading of the book shall prove my heavier burden. And so to bed, not much reassured. That night did pray I apply myself diligently to his precepts that I may gain honor as a scholar and a gentleman.

Jan. 5, 1661

Back betimes to town to confer with the President-Elect, Sir Carl Pfeiffer, on revenues for the doing of business. He, being one dedicated to the treatment of the hallucinations and phantasies of the mind, I was afeared that he be poor at figuring and the orderly keeping of accounts. To my pleasure he did discourse with greatest propriety on numbers as ever I heard in my life. Yet was grief in his words, reminding me that there be no money in the treasury to pay the clerks. My situation now being beyond discomfitture, we spoke no further words on it but repaired to the alehouse where distresses were soon forgot.

Being Twelfth Night, to home and dine with my poor wife who tells me great stories of the gossiping of the women, what this and what that woman said. It did grieve me that women should find pleasure in so spending their minds rather than in weighty discourse after the manner of men. So, in melancholy reflection, to bed.

Feb. 10, 1661

By water with Mr. Larrick to the capital where, at request of the King, the National Academy hath called a conference on the better licensing and merchandising of drugs.

In vast dismay, did learn that this year past there had come upon the market so many new medicaments - potions, philters, linaments, dotes, antidotes and I know not what - as were beyond counting. Some say they number 14,000. And there was this man saying his medicine doth cure this and another that his cures that and each the best that has yet been contrived to its purpose. So came I to be persuaded no man should longer be distressed of any illness, so many were the means of cure. Yet remains much sickness abroad such as must confound these advocates.

Some there were who argued all drugs should be suppressed by law, opining that Nature hath more cunning in healing than all the apothecaries in the land and that many medicines do produce more disease than they do cure. This sat not well with Sir Karl Beyer who was quick to reply that free enterprise may not be restrained by such contentions and if it be true there be ills that are caused by drugs this should but serve to make the chymists more zealous to find new medicines to cure the errors of the old.

A third policy that did find favor amongst some, was that new medicines be limited only to three for each disease, chosen from all that are brought to market: the choosing to be done by lottery and the King to ordain a National Drug Festival for the doing of it. Thus would the interests of all the people be served. Free competition in production would be preserved, the sacred right of free choice of drugs by the sick would be protected while all healthy citizens would find distraction in the gaming of the lottery.

The Conference came to no determination on what to do and I did leave the meeting much troubled.

Thence to the salon of the Lady Gertrude Stein and gave an accounting of my distress at the multiplying of drugs without control. She did give me much comfort persuading me that, when all be said, "a dose is a dose is a dose."

At the salon a man, of fine figure and dressed most prettily, did accost me and expound upon the ethics of these matters telling me he was a physicist and therefore spoke with authority on all matters touching human behaviour. I gave him no word back till he did speak in scorn of Hippocrates. So was my heart filled with spite as much as it could hold and there was furious conflict between him and me in words very bitter, for which God forgive me.

My worthy friend, Sir Chauncey de Leake did overhear my choler and, taking my arm, did convey me away from this coxcomb and enticed me that I go with him to the Cosmos Coffee House.

Here was fair dinner though the venizen be palpable mutton, and most excellent pleasant company. Sir Chauncey was in high pitch of mirth, a mighty talker which I did suspect before.

There was good discourse of the vanities and vices of the Court. Among the rest that the King is much discomforted by the report of his commissioners on the state of the National Institutes of Wealth. All which is duly expounded in the Dow Jones Report which now be in public circulation. It is charged therein that there be such reckless spending of the King's moneys on projects of no profit that the currency of medicine is far gone in uncontrolled inflation. One, Mr. Otto Krayer, an excellent humored man and most knowing, did concur, affirming that our physicians do pursue new projects to such exclusion of all else that none are left to teach or to tend the hospitals. Prettily did say the time had come that scholars should no longer be called Professors, but were better named Projectors.

Talk went on but, being past midnight, did leave.

Mar. 20, 1661

Up by candlelight and to the office where is much business to be done for the Annual Meeting but two weeks hence. Spring being in the air, had much conflict with myself, my heart tempting me a thousand times to go abroad about some pleasure or other. But I did not budge and, to my great content, did finish my business.

Apr. 1, 1661

Did lay long abed till roused by Lord Gilman who brought me the draft of his Presidential Address counselling that I read it and correct that which may be misspoken in phrase or in grammar. So, without eating or drinking till three in the afternoon did finish it. It was a cunning piece but were sadly ill-spelled and weak in reasoning. Methinks, My Lord is a man of mighty labor in reading and memory but the worst judge of the laying

together of what he hath read. Coming from home, by foot to the Club, where did find one, Mr. Chen, a most upright and ingenious apothecary. With him good talk of the distresses of our schools of medicine. He did outline to me a scheme, most fantastical, for the making over of medical education, conceived and planned by the merchandizers of drugs. Their argument it doth appear, is that medicine may best be taught by pictures whereby learning from books, lectures, experiments, clinics and arguments shall no longer be necessary and much time may be saved to the student. These merchandizers have ready prepared books of pictures by the best artists which they will circulate to all students and physicians. Also they have trained a great company of itinerant professors who they will send over the land with lectures learned by heart to interpret the pictures to all who will listen to them. These wandering professors are the very same as have hitherto been known to me as detail men and held in little account. When I did ask of him what training these men have had in medicine it was his reply that it was more important that they be cunning in the art of persuasion in the use of medicines than that they be wise in the diagnosis and treatment of disease. For such reason schools of medicine may soon give place to schools of Business Administration and the degree of Ph.D. to that of Dh.P. which, he instructed me, stood for Doctor of Hidden Persuasion.

When Mr. Chen inquired of me what I did think of it I could only give him words from the Holy Book that like "The Peace of God it passeth all understanding". Then, remembered it be All Fools Day, and Mr. Chen might be afooling me.

Apr. 9, 1661

By coach to Atlantic City where was the greatest confluence of scholars ever I did see. All inns were crowded and the alehouses likewise. Most kindly, My Lord did arrange a cot for me in the room which he had long engaged.

Instructing me in the manner of the assemblage, its purpose was that each scholar should learn from his fellow what the other was working on and to what purpose, so that communication of knowledge and ideas may be fostered and each scholar may return to his home with fuller understanding than he came.

Truly, I did observe there was much discourse by groups of two and three, both loud and vehement and, to my ears, ofttimes incoherent. Yet it did seem to me each scholar was more purposed to tell that which he himself had discovered than to listen to the discoveries of those with whom he held converse.

By chance, came upon Monseigneur Schmidt, chaplain to the Society. An earthy cleric but said to be a pretty fighter of the devil. Gave me good accounting of many pilgrimages to foreign parts and of the strange ways of medicine men in other lands. The more, the Ministry hath voted large funds

for the transporting of pilgrims to a big palaver which shall be in Stockholm next year. Quickly I did offer to accompany him if ship and board be found for me. Sad his reply, that care must first be given to the organizers and officials of the convention and their wives. He did fear little would be left over for the needs of other pilgrims. Seeing my discomfiture, he being kindly of heart, did promise to appoint me an organizer if such can be done discretely.

So, after many pleasant encounters on the boardwalk and sundry drafts of sack, most deviously to my cot.

Apr. 11, 1661

Up betimes that I may prepare for and attend the Business Meeting of the Society. It proved the most scandalous unparliamentary affair as ever I did see. There was much heat and fury, some complaining of the high cost of the Journal, others of delay in publishing. Some would impeach the editors that they do reject all scholarly speculations while accepting mundane compilations of measurements that have no meaning to them. Greatest excitement came with agitation by some that the name of the Society be changed, arguing, after the habit of Lord Bacon, that the more we do circumscribe and constrict our learning the more shall we know. Of contrary opinion were many who did protest that if medicine be content to learn more and more about less and less, shall end only in knowing all that can be known about nothing - a state that none would seek less he be an Existentialist. A sorry conflict and know not what issue will come of it.

In all this hub-bub I was able to conduct the elections as instructed by the President in such manner that none knew how it had been done yet took no exception to the outcome.

So, it being past time for dinner, all business was quickly dispatched after some fashion and the company adjourned. Thence to a merry dinner with van Dyke, Seevers and others till Sir Pete Geiling come to join us, whose pain in losing election to be representative to the National Research Council, made him no good company for himself and spoiled ours.

Apr. 12, 1661

Lay long abed, till aroused by a message that my wife was come to the inn to find why I am so long away from home and what I am up to abroad. Coming down to her, I found her in most sorry mood and hot for argument, charging that I have forgot this and forgot that and, like, I had forgot her. I did appease her, poor wretch, with fair words and the promise of an Easter bonnet, and give her the money for the buying of it. Though it

will cost me twenty shillings it were worth it if it bring peace. Did also say that she should come with me to the Annual Banquet this evening in her best finery and new bonnet, the which did solace her.

These past days, have I been much worn down at meetings in smoky darkened rooms listening to many discourses spoke so indifferently bad no man could follow and gazing at projections on the wall of pictures, words and figurings that came so fast could not be read. And all the time such shuffling and whispering, such ringing of bells and flashing of red lights as would distract and confuse any company. Why things are so ordered is past conjecture, though one said in jest that it is all in competition for a prize to him that can show the most slides in ten minutes.

After these tiring days the banquet gave much promise of ease and merriment yet did it fall out sadly. Seated to my left was a most comely lady fit for gallantries while on her further side the worthy Seevers. He gave her such good talk of monkeys and the tricks he taught them that she had eyes only for him, and, to my discomfiture, no words for me. So was I well content when dinner was over and the President silenced Seevers and all that we may hear the speeches.

My Lord spoke right gaily and introduced one Bishop Cannan, unknown to me, but seemed a worn and fretful cleric, who was chosen to give the sermon. He spoke on "Sacred and Profane Science," a seemly subject yet was he full of vain words, dull and overlong. I did miss the most of it, troubling myself with the high price of my wife's bonnet. I did also observe that My Lord Gilman slept much of the time but prudently did wake as it was over, gave graceful acknowledgement and spoke most cunningly as though he had heard and understood every word of it.

With this benediction made, My Lord invited a goodly company to The Dennis for punch, I and my wife with them. Though I remained in little pitch for merriment, my spouse did join in the singing and dancing with a spirit, me thought, beyond that becoming to the wife of a scholar. But I did not chide her, poor thing; she hath few occasions for gaiety.

So remained till past midnight when did hire a watchman to light us afoot back to the inn. My wife, with so much dancing, was exceeding troubled in her new shoes, and I vexed to go slow. So to bed, without prayers which never did I yet.

Apr. 14, 1661

My Lord, with grief did tell me how a messenger, on horse, had come to him from his dean with summons that he return to his College forthwith where he has not been these past six weeks by reason of meetings, conferences, committees, project visits and the like. Did assure me he would

execute the year's business of his department with all dispatch and would rejoin me in the capital inside two weeks.

May 1, 1661

My Lord, duly returned from his College, had much news of his affairs, how he had completed several applications to the National Institutes of Wealth for new grants, amongst others of a cooperative screening program which would assure him large funds and greater opportunity for travel. Decision had not yet been made as to what should be screened but My Lord foresaw no trouble in the determining of this when the grant be made.

He spoke in high praise of his students who, in his absence, had been most diligent in their projects and in the writing of papers. Though he had found no time to read these or to examine the data, he had most graciously consented to be senior author. They were most eminent contributions to knowledge and would bring him much credit.

To the Cosmos where did fall in with a goodly company of the King's advisers. Much talk of the need for more scientists to serve the nation, to wit, more chemists, physicists and engineers to produce more missiles to affront our enemies abroad and more gadgets and notions to keep our people contented and happy at home.

This did give food for thought it be these same chemists and engineers do so pollute the air the people breathe, the water they drink and the food they eat that those who guard the public health be desperate for a new kind of scientist to put right the excesses of the old. Yet it be the physicists and engineers that alone do have the ear of the King. Some speak for the need for a national science policy but, me seems, the nation's science is too important a matter to be left to the physicists. But deeming discretion the better part of valor among such courtiers, I did hold my silence.

Touching these matters, there was talk of a new cult known as systems engineers who do set themselves up to find a formula mathematical for any operation or activity of man, which through the magic of a computer machine will unfold the proper ordering of any affair be it the sailing of a ship, the running of a hospital or the management of research.

This led to a pretty story that St. Peter had asked the Academy to survey the affairs of heaven and advise upon its better management. Lord Detlev did himself direct the study and deliver the report, the which found favor with St. Peter and the Apostles. But naught came of it because, so 'twas rumored, Jehovah was unwilling to accept the Vice Presidency. Did fear My Lord might be discomforted by this story but he took it right merrily.

June 30, 1661

This being the end of the year for the schools did, for good husbandry, send out bills to all delinquent in dues, though did expect little profit of it.

It being, also, my birthday, do find myself in good condition of health and estate and well content of the honor I have received for my diligence in office. Blessed be to God, did quit the drinking of wine since the Annual Meeting, so do find myself in more even health, do mind my business better and do spend less money - and less time lost in idle company.

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Dr. Cannan concluded his readings on this pharmacological note, reflecting that the members, at their pleasure, might choose to find in these echoes of the past a cautionary tale or merely "just a little madness in the spring."

DR. DOUGLAS GOLDMAN: AFTER-DINNER SPEAKER AT 1961 FALL MEETING

Dr. Douglas Goldman, Clinical Director at the Longview State Hospital in Cincinnati and Assistant Clinical Professor of Psychiatry at the University of Cincinnati, will be the principal speaker at the dinner of the Pharmacology Society to be held on Wednesday evening, August 30, in the Women's Residence Center on the campus of the University of Rochester.

The title of Dr. Goldman's address will be "Clinical Pharmacology and Psychiatry." The very extensive experience that he has had in the clinical evaluation of tranquilizing agents should make Dr. Goldman's presentation a most interesting and enjoyable one.

SCHEDULE OF SESSIONS

Fall Meeting, Rochester, N. Y., August 29 - September 1, 1961

MORNING - 9:00 A.M.

	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
Upper Strong Auditorium		Teaching Institute -- Hogben		
Lower Strong Auditorium	Autonomics I -- Furchgott		Autonomics II -- Kuperman	SYMPOSIUM: Polypeptides -- Walaszek
Todd West	Cardiovasc. I -- Roberts		Cardiovasc. II -- Doull	
Lattimore 109	Nerve-Muscle I -- Holland		Analgesics -- Woods	
Dewey 114	Psychopharm. I -- Clark			
Bausch & Lomb Lecture Hall	Endocrinology -- Van Arman		Cell. & Bio. I -- Ellis	Drug Metabolism -- Zubrod
Morey 321	Kidney & Elec. -- Cafruny		Neuropharm. I -- Kornetsky	
			SOLLMANN ORATION Lower Strong Aud. -- 11:00 a.m.	

S C H E D U L E O F S E S S I O N S

Fall Meeting, Rochester, N. Y., August 29 - September 1, 1961

AFTERNOON - 1:30 P.M.

	TUESDAY	WEDNESDAY	THURSDAY
Upper Strong Auditorium		Teaching Institute -- Hogben	
Lower Strong Auditorium	SYMPOSIUM: Catecholamines -- Trendelenburg		Autonomics III -- Standaert
Todd West			Cardiovasc. III -- Okita
Lattimore 109	Toxicology -- Lehman		Nerve-Muscle II -- Kensler
Dewey 114			Psychopharm. II -- Domino
Bausch & Lomb Lecture Hall			Cell. & Bio. II -- Busch
Morey 321			Neuropharm. II -- Rocha e Silva
	WORKSHOP SESSIONS Faculty Club -- 7:00 p.m.	SOCIETY BANQUET Women's Res. Ctr. -- 7:00 p.m.	BUSINESS MEETING Lower Strong Aud. -- 4:30 p.m.
	SMOKER Women's Res. Ctr. -- 9:00 p.m.		SMOKER Women's Res. Ctr. -- 9:00 p.m.

WORKSHOP SESSIONS

Tuesday, August 29, 1961 - 7:00 to 8:30 p.m.
University of Rochester
Rochester, New York

Two informal workshop sessions have been scheduled for the Rochester meeting and will run concurrently on Tuesday evening from 7:00 to 8:30 p.m. They are entitled :

"Toxicological Procedures." The discussion leaders for this workshop will be Dr. Kenneth P. DuBois (University of Chicago) and Dr. Julius M. Coon (Jefferson Medical College). It is planned to conduct a discussion of the various toxicological problems of present importance and some of the new areas in which pharmacologists trained in toxicology can contribute. The approaches now used for assessment of the toxicology of chemical agents will be discussed as a preface to consideration of the manner in which various recent developments in pharmacology and related disciplines might be employed in toxicological research. An effort will be made to illustrate the direct applicability of basic knowledge concerning pathways for drug metabolism, mode of action, etc. toward progress in the understanding of species differences in susceptibility to toxic agents.

"Renal Pharmacology." The discussion leaders for this workshop will be Dr. Irwin M. Weiner (Johns Hopkins University) and Dr. Frederick E. Shideman (University of Wisconsin). The discussion will be concerned with the effects of the kidney on drugs (excretion rate, metabolism, etc.) as well as the effects of drugs on the kidney (diuresis, inhibition of active transport, uricosuric activity). Particular attention will be paid to those instances where the renal handling of a drug modifies the renal effects of the drug. Discussion of techniques will be included where pertinent.

The intent of these workshops is to make available to the advanced student of pharmacology and to those who have recently received their graduate degrees an opportunity to discuss specific areas of knowledge on an informal, but highly technical, basis with experts in those fields. In order to accomplish this, attendance at each session will be limited to 15 qualified individuals who have registered for the sessions in advance. Therefore, applications for attendance at these discussions will be handled on a first-come first-served basis and should be received in the Secretary's office by August 15, 1961. Confirmations will then be sent to accepted participants.

TEACHING INSTITUTE

Wednesday, August 30, 1961
Upper Strong Auditorium
University of Rochester
Rochester, New York

"Gastrointestinal Pharmacology"

Chairman: Dr. C. A. M. Hogben
Department of Physiology
George Washington University
Washington, D. C.

Morning Session

1. Introduction	Dr. C. A. M. Hogben Department of Physiology George Washington University School of Medicine
2. Control of Gastric Secretion	Dr. Frank P. Brooks Department of Physiology University of Pennsylvania School of Medicine
3. Gastrointestinal Motility	Dr. John T. Farrar Department of Medicine Cornell University Medical School

Afternoon Session

4. The Physiology of Smooth Muscle	Dr. Jean M. Marshall Department of Pharmacology Harvard Medical School
5. Coordination of Smooth Muscle Activity	Dr. Alexander Bortoff Laboratory of Research in Ophthalmology Western Reserve Medical School
6. Pharmacology of Smooth Muscle	Dr. Ian R. Innes and Dr. Mark Nickerson Department of Pharmacology University of Manitoba Faculty of Medicine

SYMPOSIA PROGRAMS
1961 Fall Meeting, Rochester, N. Y., August 29 - September 1

SYMPOSIUM: Release of Catecholamines

Tuesday, 1:30 P.M.

Lower Strong Auditorium

Chairman: Ullrich Trendelenburg

1:30 Introduction. U. Trendelenburg. Harvard Medical School, Boston.

1:35 Studies on the storage and release of the catecholamines of the adrenal medulla. W. R. Burack. Harvard Medical School, Boston.

2:00 Discussion.

2:10 The uptake, release and metabolism of H^3-norepinephrine and H^3-epinephrine. J. Axelrod. National Institutes of Health, Bethesda.

2:40 Discussion.

2:50 Chronotropic action of reserpine and guanethidine in the heart-lung preparation of the dog. O. Krayer. Harvard Medical School, Boston.

3:10 Discussion.

3:20 Intermission.

3:30 The release of catecholamines from the isolated heart by mephentermine. C. R. Swaine. Woman's Medical College, Philadelphia.

3:45 Discussion.

3:55 Release of catecholamines from nerve endings as a mechanism of drug action. M. Nickerson. University of Manitoba, Winnipeg.

4:20 Discussion.

SYMPOSIUM: Pharmacologically Active Polypeptides

Friday, 9:00 A.M.

Lower Strong Auditorium

Chairman: Edward J. Walaszek

9:00 Drugs that modify actions of pharmacologically active polypeptides. E. J. Walaszek. Kansas University Medical Center, Kansas City.

9:15 Questions.

9:20 Recent progress in vasopressin and oxytocin research. H. B. van Dyke. Columbia University, New York.

9:40 Questions.

9:45 Possible mechanisms of action of angiotensin. P. A. Khairallah. Cleveland Clinic.

10:05 Questions.

10:10 Chemical and pharmacological studies on the vasopressor polypeptide substance A. C. G. Huggins. Kansas University Medical Center, Kansas City.

10:25 Questions.

10:30 Bradykinin and other related kinins. P. S. Guth. Tulane University, New Orleans.

10:50 Questions.

10:55 Effects of substance P on neuronal activity. W. A. Krivoy. Baylor University, Houston.

11:15 Questions.

11:20 Properties of a polypeptide formed by the incubation of cerebral spinal fluid with globulin. L. F. Chapman, A. O. Ramos and H. G. Wolff. Cornell University, New York.

11:40 Questions and general discussion.

ABSTRACTS

of Scientific Papers Presented at the
Fall Meeting
of the

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

August 29 - September 1, 1961
University of Rochester, Rochester, N. Y.

TUESDAY MORNING

AUTONOMIC PHARMACOLOGY I
Lower Strong Auditorium

COMPARATIVE ACTIVITY OF SYMPATHOMIMETIC AMINES (SYMPAM) ON RABBIT AORTIC STRIP AND BLOOD PRESSURE (BP). M. Wurzel**, T.P. Pruss*, T. Koppanyi and G.D. Maengwyn-Davies. Dept. of Pharmacology, Georgetown Univ. Schools of Med. and Dent., Washington, D.C.

Dose-response curves to SYMPAMs on the isolated aortic strip (Proc.Soc.Exp.Biol.Med. 1960,105:659) and on BP were obtained and potencies relative to norepinephrine (NOR) compared. A. Aortic strip. 1) The chemical structures associated with strongest contractile activity are: a) phenyl ring with m-OH; b) amino head -NH2, or -NH-Me without α-methyl in the ethyl chain. Dopamine is an exception: N-Me or β-OH substitution increase its potency unexpectedly; intramolecular factors might be held responsible. 2) Maximal contractions obtainable with compounds of potency less than 1/250 diminish with decrease in potency. 3) Dichloro--NOR and tachyphylactogenic amines show bellshaped dose-response curves, i.e. high concentrations give submaximal contractions. B. Comparison of aortic strip and blood pressure responses. SYMPAMs can be classified into four groups: I. equally effective on strip and on BP, like NOR, epinephrine; II. more effective on strip than on BP, like epinine, norphenylephrine; III. less effective on strip than on BP, like ephedrine, tyramine; IV. compounds ineffective on strip are depressors. SAR of SYMPAMs and the possible involvement of other organs and of humoral factors in rabbit BP responses will be discussed. (Supported by grant B-1448, NINDB, USPHS. *Schering Corporation Fellow.)

COMPARISON OF THE INFLUENCE OF COCAINE AND OTHER LOCAL ANESTHETICS UPON THE ACTION OF NOREPINEPHRINE AND TYRAMINE. W. H. Macmillan and Allan Kupferman*. Dept. of Pharmacology, Univ. of Vermont, Burlington, Vt.

Many commonly used therapeutic agents alter sympathetic activity. Among this group are the local anesthetics and antihistaminics. A comparative study has been made of the actions of phenacaine, lidocaine, procaine and tripelennamine with cocaine upon isolated rabbit atria. All of these agents in a concentration of 1×10^{-8} to 1×10^{-6} can be shown to reversibly depress the spontaneous atrial rate and potentiate the action of norepinephrine. Concentrations greater than 1×10^{-5} irreversibly depress the atria. A primary difference between cocaine and the other agents studied was found in studies on the spinal cat. While cocaine potentiates the action of norepinephrine and depresses the action of tyramine upon blood pressure, spleen volume and nictitating membrane response, phenacaine, lidocaine, procaine and tripelennamine potentiate the actions of both norepinephrine and tyramine. The contribution of impaired nerve conduction induced by these agents has been considered in determining the possible mechanisms by which they alter sympathetic activity.

BLOCKADE OF REFLEX DILATATION BY ERGOT ALKALOIDS. Lloyd Beck*, Dept. of Pharmacology, U. of Mich. Med. School, Ann Arbor, Mich.

Dihydroergocornine methanesulfonate (DHEC) in a dose of 2-4 microgram/kg, blocks active reflex dilatation in the perfused hindquarters of the dog. Reflex dilatation produced by sinus nerve stimulation can be also reduced or blocked by low doses of DHEC. Preliminary experiments using the cross-circulated head preparation indicate that reflex dilatation can still be elicited after administration of DHEC to the recipient head. Such doses of DHEC 1) fail to produce significant adrenergic blockade to injected norepinephrine; 2) fail to reduce the constrictor effect produced by efferent lumbar sympathetic stimulation; and 3) fail to block reflex constriction produced a) by tracheal occlusion, b) by strong afferent vagal stimulation, or c) by the injection of an intravenous dilator. In low doses DHEC does not affect the dilatation produced by intra-arterial injection of histamine, methacholine, glyceryl trinitrate, isoproterenol, ATP, ADP, AMP, adenosine, substance P or bradykinin. It is concluded that DHEC must selectively block either transmission in the efferent limb of the dilator system, or the release of the dilator substance from the sympathetic nerve endings, or the effect of the released dilator on the blood vessels. (Supported by USPHS Grant #H-3946).

RELATIVE HYPERGLYCEMIC ACTIVITIES OF SYMPATHOMIMETIC DRUGS IN INTACT RATS. William W. Fleming and Alexander D. Kenny. Department of Pharmacology, West Virginia University Medical Center, Morgantown, W. Va.

In comparing the relative hyperglycemic activities of sympathomimetic amines in fasted rats it was found that at low doses isoproterenol is more potent than epinephrine in raising the blood glucose 1 hour after subcutaneous injection. At higher doses, however, epinephrine is more potent than isoproterenol, as the response to the latter reached a maximum level of 28 mg/100 ml above the control rats. In the dose range studied norepinephrine was the least potent drug.

	Increase in Blood Glucose, mg/100 ml						
Dose, mg/kg	.002	.005	.01	.02	.10	.20	.50
Isoproterenol	2	13	21	28	-	28	28
Epinephrine	-	-	4	13	47	83	113
Norepinephrine	-	-	-	-	2	8	24

If the Ahlquist theory of α and β receptors pertains to the hyperglycemic response, the results of this study indicate that at low doses β receptors may be predominant. (Supported by grants from NIH, B3034 and A4276).

DOES DCI BIND ALPHA-RECEPTORS? I. H. Slater and G. T. Jones.* Eli Lilly Research Laboratories, Indianapolis, Indiana.

Hull, Eltherington and Horita have suggested that DCI activates α-receptors as well as blocking β-receptors while functioning as a partial agonist. In anesthetized cats, DCI restored the pressor response of epinephrine after partial blockade with dibenzyline. It has been established that potent agonists, such as norepinephrine, will protect α-receptors from inhibition by chlorethylamine adrenergic blocking agents. We have confirmed this finding on isolated guinea pig vas deferens using the technique of Leach. DCI potentiated norepinephrine responses in this tissue. Isoproterenol inhibited norepinephrine-induced contraction. DCI, in doses sufficient to block this effect of isoproterenol, did not interfere with the development of a blockade by a chlorethylamine-blocking agent (08353). The guinea pig vas deferens apparently contains both α- and β-adrenergic receptors. Doses of DCI adequate to block the β-receptors do not protect the α-receptors, suggesting that α-receptor interaction with DCI is probably not an important part of the action of DCI.

FURTHER STUDIES ON THE RELEASE OF CATECHOL-AMINES FOLLOWING COMMON CAROTID CLAMPING IN INTACT AND ADRENALECTOMIZED DOGS. William J. Coffey, Jr.* and Walter M. Booker. Dept. of Pharmacology, Howard Univ. School of Med., Washington, D. C.

Previous experiments from our laboratory have shown that common carotid clamping results in marked increase in catecholamine secretion from the adrenal gland concomitant with blood pressure elevation. Also in the adrenalectomized animal, although the blood pressure does not rise as high following clamping of carotids as in the intact animal, the femoral artery blood samples show a higher amount of catechol-amines. In addition to these observations, it appears that during carotid clamping in intact animals there is a significant increase in the catechol-amines coming from the brain. Extension of these experiments has confirmed our earlier observations, and we are now conducting experiments with P-286 in intact dogs (anesthetized) and with dibenzylene and reserpine in adrenalectomized dogs. It appears that the dibenzylene treated animals do not show blood pressure elevation on carotid clamping, and there is no elevation of catechol-amines in femoral artery or vein blood. P-286, specific for blocking secretion of the adrenal medulla, appears to be limited in time as to its prevention of catechol-amine secretion during carotid clamping. Experiments involving the isolated perfused head (Heymans) will be reported.

FATE OF H^3-NOREPINEPHRINE AT THE SYMPATHETIC NERVE ENDINGS. Georg Hertting* and Julius Axelrod. Laboratory of Clinical Science, Natl. Inst. of Mental Health, Bethesda, Maryland.

Previous work in this laboratory has shown that H^3-norepinephrine is selectively taken up and retained at sympathetic nerve endings (Nature 189: 66, 1961). H^3-norepinephrine was administered to cats and five hours later the spleen was isolated and perfused with blood from a donor cat. Whenever the splenic nerve was stimulated, large amounts of H^3-norepinephrine were released into the blood stream. The O-methylated metabolite of H^3-norepinephrine, H^3-normetanephrine, was also elevated after each series of stimuli. Very small amounts of deaminated catechols were found in the outflowing blood and no rise in these deaminated products could be detected after stimulation. Injection of nonradioactive norepinephrine caused a sharp contraction of the spleen, but no rise of H^3-norepinephrine and H^3-normetanephrine was found. A number of drugs were found to affect the release of H^3-norepinephrine from the nerve endings. It can be concluded that circulating H^3-norepinephrine is taken up by the sympathetic nerve endings and released on stimulation, and the released neurohumor is then metabolized by catechol-O-methyltransferase, rebound by the nerve endings or discharged into the blood stream.

EFFECT OF NONCATECHOLAMINE SYMPATHOMIMETICS ON PLASMA CATECHOLAMINES. Stewart C. Harvey and Tom S. Sulkowski*. Dept. Pharmacology, Univ. Utah College of Med., Salt Lake City.

Arterial pressure (b.p.) and heart rate of spinal dogs were recorded. Blood samples were taken from femoral vein before, at peak b.p. response after a drug, then at 4-min. intervals until the b.p. response waned, and finally after stabilization. Catecholamines (c.a.) were assayed by the E.D.A. method. Controls showed 0.7±0.3 μg/l epinephrine and 2.9±1.2 μg/l norepinephrine. Amphetamine SO_4 (Fleckenstein Group III), 1-5 mg/kg, and ephedrine SO_4 (Group II), 0.5-2 mg/kg, elevated c.a. levels by increments as much as 6 μg/l epinephrine and 28 μg/l norepinephrine, the increment in norepinephrine usually being the larger. Amphetamine induced larger increments than ephedrine at equipressor doses. Peak increment usually came later than peak b.p., and c.a. levels sometimes remained high after b.p. returned to baseline. Norepinephrine levels returned to normal more rapidly than epinephrine levels. In one dog with a depressor response to amphetamine, only a slight rise in c.a. levels occurred. Phenylephrine (Group I) sometimes lowered and sometimes raised c.a. levels. Tuaminoheptane lowered norepinephrine and raised epinephrine levels in one dog. Other drugs are being studied. (Aided by N.I.H. grant 2G-153 and Utah Heart Association.)

FURTHER EVIDENCE THAT DOPA-MINE MAY GO RAPIDLY TO NOR-EPINEPHRINE IN VIVO. Rafael Linares*, William West*, Jeannette Bryant*, and Walter M. Booker. Dept. of Pharmacology, Howard Univ. School of Med., Washington, D. C.

We have presented many lines of evidence that infused DOPA-mine in intact dogs may go (although in small percentage) to nor-epinephrine in ten to twenty minutes. Also brain or adrenal slices incubated in DOPA-mine solutions synthesize nor-epinephrine rapidly. Our work continues along the following lines:

1) Infusion of DOPA-mine into intact or adrenalectomized animals, treated (or untreated) with reserpine and/or adrenergic blocking agents.
2) Infusion of DOPA-mine into dogs (with adrenals) following treatment with P-286.
3) Administration of DOPA-mine into a receiver dog (perfused head technique) via the carotid anastomosis.
4) Administration of alpha-methyl DOPA to animals prior to incubation of brain slices.
5) The role of the mono-amine oxidase inhibitors in nor-epinephrine synthesis in brain.

Results and possible interpretations of the above will be given.

ACTION OF ADRENERGIC AGENTS ON INTRAOCULAR TENSION IN RABBITS. Edward Alpert*, Henry Jacoby*, David Reinke*, and Donald R. Bennett. Dept. of Pharmacology, Univ. of Mich., Ann Arbor.

Bitartrate salts of l-norepinephrine (I), l-epinephrine(II), or l-isoproterenol (III) produce ocular hypotension in normal trained unanesthetized rabbits (single blind procedure). Tension was measured by a tonometer after .5% topical tetracaine. Drugs were dissolved in .9% NaCl with .1% $NaHSO_3$, and applied topically in a constant volume of .05 ml within 10 min of preparation. Control tensions range from 20-28 mm Hg, (Schiötz tonometer calibrated for rabbit). 2% I and II, and .5% III cause an average fall of 7-8 mm Hg within 3 hours with a return to normal in about 24 hours. As little as 2.5 ug III produces a hypotensive response. To produce equal responses, the potency order is III>II>I. 0.5% cyclopentolate and 1% pilocarpine are ineffective. Phenylephrine (IV), hydroxyamphetamine (V), and ephedrine (VI) produce a hypotension but are less potent than I, II, or III. The d-isomers of I, II, or III are much less potent than IV, V, or VI. II is not antagonized by 24 hr pretreatment with 2 mg/kg i.v. phenoxybenzamine. One hr pretreatment with 10 mg/kg i.m. dichloroisoproterenol antagonizes I, II, or III. Chronic superior cervical postganglionic sympathectomy enhances the response to I, II, or IV; abolishes the response to V and VI; but does not alter the response to III. (Supported by USPHS Grant #SF 76).

A COMPARISON OF THE EFFECT OF GUANETHIDINE AND HEXAHYDRO-1-AZEPINEPROPIONAMIDOXIME HCl (SU-4029) IN SOME SYMPATHETIC PATHWAYS. R. A. Maxwell. Research Dept., CIBA Pharmaceutical Products Inc., Summit, New Jersey.

Guanethidine and Su-4029 suppress the pressor responses elicited by stimulation of the left greater splanchnic nerve in cats which have had the ipsilateral adrenal removed. Both guanethidine (McCubbin et al, J.Pharmacol. & Exper.Therap. 131: 346, 1961) and Su-4029 change the vasoconstriction evoked in the hind limb of dogs by stimulation of the lumbar sympathetic chain to vasodilation. Su-4029 depletes the heart and aorta of dogs of their catecholamine content. A similar depleting action has been reported for guanethidine (Cass et al, Proc. Soc. Exper. Biol. & Med. 103:871, 1960). However, Su-4029 does not interfere with the contractions of the nictitating membranes of cats which are elicited by preganglionic stimulation of the cervical sympathetic trunk; guanethidine interferes markedly with these contractions. In unanesthetized dogs and cats, Su-4029 does not relax the nictitating membranes while guanethidine produces profound relaxation of the membranes in both species. The data suggest that guanethidine and Su-4029 produce blockade by a similar mechanism in several sympathetic pathways, but in at least one pathway, Su-4029 is ineffective.

CARDIOVASCULAR PHARMACOLOGY I
Todd West

CARDIAC EFFECTS OF SYMATHOMIMETIC AMINES. C. Mendez and D. Erlij*. National Inst. Cardiol., Mexico

Effects of sympathomimetic amines and of dichloroisopropylarterenol (DCI) upon heart rate, A-V and ventricular functional refractory periods (RP) and ventricular conduction time (CT) were studied in denervated dog hearts. Isopropylarterenol (0.3γ/kg/min) caused acceleration of the heart and shortening of the A-V RP equivalent to epinephrine (2.5γ/kg/min), but caused less shortening of ventricular RP and did not shorten CT. Phenylephrine had little effect upon sinus frequency and A-V RP at a dose level (20γ/kg/min) which markedly influenced ventricular RP and CT. Methoxamine in single doses of 225γ/kg caused only shortening of the ventricular RP and CT. DCI (9 mg/kg) blocked effects of epinephrine upon frequency and A-V RP, partially blocked effect on ventricular RP, and did not prevent shortening of ventricular CT. These data suggest that adrenergic effects upon various cardiac properties studied are mediated through distinctly different receptors.

ANTAGONISM BY METHOXAMINE OF THE INOTROPIC AND CHRONOTROPIC ACTIONS OF CATECHOLAMINES. John R. Blinks.* Department of Pharmacology, Harvard Medical School, Boston, Massachusetts.

Dose-response curves for the inotropic and chronotropic actions of l-arterenol, l-epinephrine, and l-isoproterenol were determined on isolated guinea pig atria (Blinks: Fed. Proc. 19:88, 1960). Methoxamine HCl, in concentrations above $5X10^{-6}$M, effectively antagonizes both actions of all three catecholamines, producing a parallel shift in the log dose-response curves without a significant change in the maximum response to the agonist. The inotropic and chronotropic actions are affected similarly. In a concentration of $5X10^{-4}$M, methoxamine shifts the dose-response curves for each of the catecholamines by a concentration factor of about 100. The positive chronotropic action of histamine (Trendelenburg: J. Pharmacol. 130:450, 1960) is not antagonized by methoxamine. In concentrations which are effective in antagonizing the actions of the catecholamines, methoxamine has moderate negative inotropic and chronotropic actions of its own. (Supported by USPHS grants H3738 and H2205.)

INDUCTION OF VENTRICULAR AUTOMATICITY BY INTRA-ARTERIAL INJECTION OF ISOPROTERENOL. Peter E. Dresel, M.C. Hart* and B.C.R. Strömblad*. Fac. of Med., University of Manitoba, Winnipeg.

We have questioned recently the role of increases in ventricular automaticity in the induction of certain cardiac arrhythmias in hydrocarbon-sensitized dogs. Threshold doses of isoproterenol for induction of arrhythmias when injected into the left coronary arteries have now been determined. In barbiturate anesthetized dogs, doses of 0.1 to 1.0 μg into the circumflex branch resulted usually in AV-nodal rhythm, while doses as large as 10 μg had no effect when injected into the descending branch. In cyclopropane-anesthetized animals the range of threshold doses after circumflex artery injection was the same as in non-sensitized dogs. Injections into the descending artery of sensitized preparations caused arrhythmias, the threshold dose range being the same as in the circumflex branch. Changes in blood pressure had no effect on thresholds under pentobarbital anesthesia. Increases in systemic pressure decreased the thresholds determined in either artery under cyclopropane, while decreases in blood pressure had the opposite effect. Results under ether anesthesia are identical to those obtained under pento barbital. These results indicate two apparently qualitative differences between sensitized and non-sensitized preparations. (Supported by grants from the National Research Council of Canada and the American Heart Association.)

THE EFFECT OF CATECHOLAMINE RELEASING DRUGS ON CATECHOLAMINE UPTAKE BY THE HEART. T. E. Gaffney,* G. Acheson and J. Peagler.* Natl. Heart Inst., Bethesda, Md., and Univ. of Cincinnati, College of Medicine.

Though chronic administration of reserpine or guanethidine decreases myocardial catecholamines (CA), it is not known if they affect myocardial CA uptake. The increases in heart rate (HR) and contractile force (CF) produced by acute guanethidine in the normal heart-lung preparation (HLP) are absent in the reserpine-pretreated HLP and are therefore presumably dependent upon release of stored CA. This suggests the use of the response to acute guanethidine as a test for the presence of stored amines. In HLP's made from reserpine-pretreated dogs, norepinephrine 24 to 400 μg, infused over 2 to 30 minutes, caused the usual increases of HR and CF as measured with the strain gauge arch. When these responses had subsided, guanethidine, 1 or 5 mg, caused increases in HR and CF, as it does in dogs not pretreated with reserpine (10 experiments). Reserpine, 1 mg (2 experiments) or guanethidine, 1 to 5 mg (4 experiments) given before the norepinephrine infusion did not alter this result, though this preliminary guanethidine dose had no effect on HR and decreased CF, as previously reported. These results demonstrate that the presence of reserpine or guanethidine, in the doses studied, does not prevent the uptake of norepinephrine by the heart and/or lungs. The disappearance of the response to previously administered norepinephrine suggests that this CA has been destroyed but its subsequent release by guanethidine shows that the CA was merely stored.

EFFECT OF GUANETHIDINE ON THE HEART RATE RESPONSE TO SYMPATHOMIMETIC AMINES. M. H. Alper* and J. Schmier*. Department of Pharmacology, Harvard Medical School, Boston, Massachusetts.

While studying the effects of guanethidine in the dog heart-lung preparation (HLP), it was noted that, in the HLP of dogs pretreated with reserpine (2 x 0.5 mg/kg s.c. 48 and 24 hours before isolating the heart) the heart rate-increasing action of norepinephrine (NE) was greater in the presence of guanethidine than in its absence. Quantitative studies, using continuous infusions of NE and constructing complete dose-response curves, demonstrated in the normal HLP, an average ED50 for cardio-acceleration of 6.7 μg/min NE (4 exp.). In the HLP depleted of NE, the ED50 was 3.3 μg/min (5 exp.) whereas after 6 mg of guanethidine, the ED50 was 0.29 μg/min NE (5 exp.). This tenfold enhancement of the rate-increasing action of NE by guanethidine probably accounts, along with its NE-releasing action in the heart, for the rate-increasing effect in the normal HLP. Similar studies with ephedrine and phenylephrine revealed no sensitization by guanethidine to their rate-increasing action. (Supported by USPHS grants 2G-165 and H2205 and American Heart Association grant 59 G 11.)

CARDIOVASCULAR EFFECTS OF T-OCTYLGUANIDINE (BP1184). J. L. Schmidt, Hollis G. Schoepke*, H. D. Brondyk*, R. G. Wiegand* and L. H. Wiemeler*. Division of Experimental Therapy, Abbott Laboratories, North Chicago, Illinois.

T-octylguanidine is a potent new hypotensive agent. In anesthetized normotensive dogs and cats it produced a fall in blood pressure, inhibition of the carotid occlusion pressor response and potentiation of the norepinephrine pressor response. Arterial pressure of renal and neurogenic unanesthetized hypertensive dogs was lowered for periods of 24 hours or longer. Oral doses of 2 mg/kg caused prolapses of the nictitating membranes of unanesthetized cats of about 48 hours duration without pupil dilatation. In the anesthetized cat nictitating membrane preparation using pre- and postganglionic stimulation, BP1184 produced a transient (10') phase of sympathetic ganglionic blockade followed by a prolonged period of at least partial sympathetic atony. BP1184 (10^{-5} g/ml) produced a positive inotropic effect on the isolated papillary muscle of the cat which was blocked by dichloroisoproterenol and reserpine suggesting that a catecholamine release mechanism was involved. BP1184 also caused a decrease in cardiac norepinephrine levels. It is concluded that some of the hypotensive effects are due, at least in part, to a blockade of the sympathetic nervous system.

THE EFFECTS OF BRETYLIUM, GUANETHIDINE AND BETA-TM-10 IN RATS SUBJECTED TO DRUM SHOCK. Bert K.B. Lum* and Deane N. Calvert† Univ. of Kansas Med. School, Kansas City, Kansas.

Ganglionic and adrenergic blocking agents have been reported to protect animals subjected to experimental shock. In the present studies, a number of newer agents which inhibit sympathetic nervous system activity were tested in rats subjected to traumatic shock using the Noble-Collip drum. Protection against death due to drum shock was obtained by pretreatment of rats with bretylium, guanethidine or beta-TM-10 (S.K.F. No. 6890). These observations provide additional evidence that inhibition of sympathetic nervous system activity will provide protection against the development of irreversible shock. (Supported by USPHS Grant H-3762).

BLOOD PRESSURE RESPONSES TO ADRENERGIC AGENTS AND TISSUE CATECHOL AMINE LEVELS IN DOGS SUBJECTED TO HEMORRHAGIC SHOCK. Deane N. Calvert* and Bert K.B. Lum*, Univ. of Kansas Medical School, Kansas City, Kansas.

Irreversible hemorrhagic shock was produced in dogs by a modified Wigger's procedure. In all animals, the systemic pressor responses to epinephrine (E), norepinephrine (NE) and tyramine (T) were markedly diminished early during normovolemic shock. The pressor response to T remained markedly reduced throughout the period of observation. In contrast, the pressor responses to E and NE, initially depressed, gradually increased so that they approached or were equal to control (pre-shock) values 4 to 6 hours after reinfusion in most animals. The diminished response to T could be partially restored by a large dose of NE.

E and NE levels were measured in ventricle, spleen, aorta and adrenal gland following sacrifice of animals subjected to the above procedure. In the heart, spleen and adrenal the total catechol amines were found to be reduced. In contrast to these, the total amine content of the aorta was not reduced but a shift from about 90% NE to approximately 50% E was seen. The relationship between tissue amine levels and alteration of pressor responses to adrenergic agents will be discussed. (Supported by USPHS Grant H-3762).

EFFECT OF CHLORDIAZEPOXIDE AND CHLORPROMAZINE ON ADRENERGIC REGULATION OF CARDIOVASCULAR FUNCTION. R. A. Moe*, R. Banziger* and G. Zbinden. Hoffmann-La Roche Inc., Nutley, N. J.

In vitro, both preparations reduced the contractile force in isolated, electrically stimulated auricles of rabbits and inhibited positive inotropic response to l-epi. Potentiation of contractile force due to electrically evoked extra systoles (cat auricles) was reduced in proportion to negative inotropic effects without apparent loss of tissue responsiveness to fixed stimuli. In vivo, a transitory potentiation of blood pressure responses to n-epi. preceeded the inhibitory effects. Chemical analysis for brain and heart biomines in rabbits after chlordiazepoxide i.p. showed a slight elevation in cardiac tissues after single doses whereas tissues from chronically dosed animals showed no change. Further, repeated i.p. doses of both compounds did not alter the incidence of isoproterenol induced myocardial necrosis in rats. Rats given single i.p. doses of chlordiazepoxide (7.5 and 15 mg/kg) and chlorpromazine (5 mg/kg) 1 hour prior to shock and traumatic experiences in the Noble-Collip Drum appeared partially protected from deleterious effects of shock. The peripheral activities described suggest that these compounds temporarily interfere with catecholamine transfer. The effect is of short duration and does not appear sustained with repeated dosing.

PHARMACOLOGY OF 3-DIMETHYLAMINOPROPYL-THIOPSEUDOUREA·DI-HCL (BAX 495). F. T. Galysh,* R. N. Morris* and C. E. Lints.* Baxter Laboratories, Inc., Morton Grove, Ill.

Intravenous doses of 1-3 mg./kg. of Bax 495 produced a sustained 20% or greater lowering of femoral arterial pressure and an inhibition of the carotid baroreceptor reflex in 16 anesthetized normotensive dogs. In addition, doses of 25-50 mg./kg. per os lowered blood pressure of metacorticoid hypertensive rats. At hypotensive dose levels, Bax 495 partially or completely blocked feline nictitating membrane responses to preganglionic stimulation but not to injected epinephrine. Furthermore, in anesthetized dogs similar dose levels of the thiopseudourea did not inhibit or reverse the pressor responses evoked by i.v. epinephrine or norepinephrine. Large i.v. doses of Bax 495 (5-45 mg./kg.) produced cholinergic side effects in unanesthetized dogs. Prior atropinization blocked these effects but not the hypotensive response. This compound increased perfusion rate through the vasculature of the isolated hind limbs of cats and dogs. Bax 495 is a potent, relatively non-toxic hypotensive agent (i.v. LD_{50} in mice: 220 mg./kg.). Its hypotensive effects are presumably related to a peripheral vasodilatory and ganglionic blocking action.

TUESDAY MORNING

CARDIOVASCULAR PHARMACOLOGY I

VASCULAR BLOCKING ACTIONS OF ERGONOVINE. J. Henry Wills. Directorate of Medical Research, U. S. Army CR&D Labs., Army Chemical Center, Md.

As reported previously (Fed. Proc. 8: 168, 1949; 10: 148, 1951), small doses (0.1 to 1.5 mg/kg) of ergonovine maleate in the dog anesthetised with sodium pentobarbital diminish the pressor effect of N,1-dimethylhexylamine and increase that of epinephrine. Such doses of ergonovine also enhance depressor effects by N,1-dimethylhexylamine, 1-methylhexylamine or 1-ethylheptylamine. Pressor effects from N,1-dimethylcyclopentylethylamine were enhanced; a slight pressor effect from 1-ethylheptylamine became evident. Larger doses of ergonovine maleate (2.5 to 8.0 mg/kg) decrease depressor and/or pressor responses to N,1-dimethylhexylamine, 1-methylhexylamine or epinephrine.

CIRCULATORY CHANGES PRODUCED BY NA-PENTOBARBITAL ANESTHESIA IN DOGS. E. Soaje Echague.* Chemical Therapeutics Research Laboratory, Miles Laboratories, Inc., Elkhart, Indiana.

The carotid artery in 36 mongrel dogs was cannulated with polyethylene tubing under 30 mg/kg Na-pentobarbital. Blood pressure and respiration were recorded continuously for two hours after cannulation and ECG's were taken every 15 minutes. For 3 to 83 days following operation, two-hour recordings were carried out on these dogs using no anesthesia or restraining measures. Na-pentobarbital administration was repeated at the same dose, i.v. or i.p., in some of the animals and the effects followed for two hours afterwards. The average blood pressure under anesthesia was 153 ± 23 and after recovery or without anesthesia 103 ± 18 mmHg; the heart rate varied from 167 ± 34 under pentobarbital to 95 ± 26 without anesthesia. Tachycardia and bradypnea occurred immediately after the administration of the anesthetic, while the blood pressure dropped and then rose slowly, reaching its maximum 30 to 45 minutes later; it remained steady thereafter for the duration of the anesthesia. Systolic and diastolic pressures were increased but the pulse pressure decreased. The pentobarbital hypotensive effects tend to exaggerate the hypotensive activity of drugs being screened for hypotensive effects in the anesthetized dog.

NERVE AND MUSCLE I
Lattimore 109

THE ACTION OF PHENOTHIAZINES ON THE END PLATE POTENTIALS OF FROG MUSCLE. W. Schlosser* and C. P. Kraatz. Dept. of Pharmacol., Jefferson Medical Coll., Philadelphia, Pa.

End plate potentials of the nerve-muscle preparation of the frog sartorius were recorded using the moving fluid electrode method, with routine curarization by tubocurarine chloride (3.5×10^{-6}). Chlorpromazine, promazine and prochlorperazine (10^{-6} to 5×10^{-6}) reduced the amplitude of the end plate potential without effect on the nerve action potential. The depression was not reversed on removal of the drug. An increase in the Ringer calcium from 0.9 mM to 7.2 mM caused an increase in the end plate potentials following treatment by the 10^{-6} levels of the three drugs. With the higher concentrations of the phenothiazines, the same calcium increase resulted in consistent potential increases only in the prochlorperazine-treated muscles, with little or inconsistent actions in the others. (Supported by U.S.P.H.S. A-5166)

THE EFFECT OF GANGLIOSIDES ON THE MUSCLE ACTIVITY OF CHLORPROMAZINE. R. L. Irwin, H. J. Smith, III* and E. G. Trams. National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland

Gangliosides were previously found to prevent the blocking activity of d-tubocurarine on frog rectus muscle (Fed.Proc. 20:174, 1961). Since the gangliosides did not alter contraction produced by acetylcholine their activity against d-tubocurarine was believed to be due to an interaction with the drug molecule rather than tissue receptors. The present experiments have shown that gangliosides prevent the blocking activity of chlorpromazine on Ach stimulated frog rectus muscle. The contraction of this muscle produced by higher concentrations of chlorpromazine is also prevented by the gangliosides. The removal of N-acetyl-neuraminic acid from gangliosides by acid hydrolysis only partially destroys the activity of the gangliosides against the action of chlorpromazine. When kept away from the muscle by use of a dialysis bag the gangliosides prevent the activity of either d-tubocurarine or chlorpromazine. This latter finding indicates that the activity of gangliosides is related to an interaction with the drug molecules and not muscle receptors.

EFFECTS OF 2 PYRIDINE ALDOXIME METHIODIDE (2-PAM) AND 1,1' TRIMETHYLENE BIS (4-FORMYL PYRIDINIUM BROMIDE) DIOXIME (TMB-4) ON THE ISOLATED FROG RECTUS ABDOMINIS MUSCLE. Joseph H. Fleisher and Thomas H. Moen*. Army Chemical Center, Md.

The contracture of the frog rectus muscle following addition of depolarizing drugs is influenced by prior addition of 2-PAM or TMB-4. For example concentrations of 2-PAM in excess of 4×10^{-5}M potentiate contractures of the frog rectus muscle elicited by acetylcholine (Ach). This potentiation appears to result from an anticholinesterase property of this oxime and not from a direct depolarizing action. 2-PAM inhibits the response to depolarizing agents decamethonium and carbamylcholine, which are not susceptible to hydrolysis by the cholinesterase enzyme of frog rectus muscle, and also to Ach in the eserinized preparation. TMB-4 showed only inhibitory actions; these appeared stronger than those of 2-PAM on the response of the frog rectus to the depolarizers studied.

TETRAETHYLAMMONIUM STIMULATION OF SKELETAL MUSCLE BY THE RELEASE OF ACETYLCHOLINE FROM INTRAMUSCULAR NERVE ENDINGS. George B. Frank. Dept. of Pharmacol., Univ. of Manitoba, Winnipeg, Can.

In this study, results were obtained showing that threshold concentrations of tetraethylammonium (TEA) stimulated frog's sartorius muscles by releasing acetylcholine and TEA had a direct action only at much higher concentrations. The muscle response to other cholinergic drugs consisted of a small, smooth shortening, starting a few seconds after exposure to the drug. Threshold concentrations of TEA produced a strong twitching response starting usually a minute or more after exposure to the drug. Denervated muscles were less sensitive to TEA stimulation than controls and the responses produced in denervated muscles resembled the usual response produced by other cholinergic drugs. These results would be expected if there were a sudden release of acetylcholine once the TEA concentration in the extracellular fluid reached a critical level. In support, it was found that depleting the acetylcholine stores by stimulating the nerve to a muscle exposed to hemicholinium (HC-3) greatly increased the TEA threshold of that muscle over an unstimulated control muscle in the same bath. By recording from the ventral root of the IX spinal nerve it was found that TEA stimulated the muscle without producing action potentials in the motor nerve fibres supplying the muscle. (Supported by a grant from the Muscular Dystrophy Association of Canada).

TUESDAY MORNING

NERVE AND MUSCLE I

CHOLINESTERASE ACTIVITY OF DYSTROPHIC AND DENERVATED MUSCLES. James A. McFarland* and A.R.McIntyre. Univ. Nebraska Coll. of Medicine, Omaha Nebraska.

Hyperirritability, spontaneous fibrillation and very rapid "dive.bomber" activity in dystrophia myotonia in both mouse and man has been reported previously (1). The spontaneous activity of dystrophic muscles resembles that seen early following denervation and the activity is not readily suppressed by d-tubocurarine. Examination of the cholinesterase activity in muscles from dystrophic mice showed that the activity of this enzyme was much below that of normal muscles and that likewise the cholinesterase activity from denervated was also lower than that from the normal innervated opposite muscles. Muscles were quickly frozen,removed,homogenized. Aliquots of homolysate were incubated with known amounts of ACh and the rate of hydrolysis of ACh compared with normal controls and blanks. The residual ACh content remaining after various durations of incubation were assayed.(Venus mercenaria method). In no instance was the cholinesterase activity of dystrophic or fibrillating denervated muscle as great as normal muscle and was found to vary from 25% to 50% below normal. It is concluded that the cholinesterase activity of denervated and dystrophic muscle is below that of normal muscle.(Supported in part by grants from N.I.H. and Muscular Dystrophy Assoc.of Am.

1. A.M.A. Archives of Neurol & Psych. 81:678,1959.

PHOSPHORYLASE ACTIVITY IN CARDIAC AND SKELETAL MUSCLE. K.R. Hornbrook* and T.M. Brody, Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

Phosphorylase a (active) and total phosphorylase activities were measured in excised and perfused hearts. Total phosphorylase activity by the method of Cori and Illingsworth ranged from 700 units to 250 units per gram of heart wet weight in various species. In descending order activities were as follows: dog = rat > guinea pig > frog. In all species studied skeletal muscle activities were higher than those recorded for cardiac muscle. Phosphorylase a values for the anesthetized excised rat heart were approximately 25% of total. Rat hearts perfused for 20 minutes prior to freezing gave phosphorylase a values of 15%. In perfused hearts no changes in phosphorylase activity were observed when Ca^{++} concentrations were altered. Treatment of heart extracts with ion exchange resins usually lowered the phosphorylase a values. Pretreatment with reserpine, amine oxidase inhibitors, and other agents which would tend to alter cardiac catecholamine content did not seem to affect phosphorylase a activity.

CHEMICAL INHIBITION OF DIRECTLY STIMULATED SINGLE MUSCLE FIBERS. R.K. Orkand.* Univ. of Utah College of Medicine, Salt Lake City, Utah.

Conventional technics for intracellular electrical stimulation, intracellular potential recording, and measurement of tension responses were utilized to determine the relation between membrane potential, transmembrane current, and contraction in single fibers from the contractor epimeralis muscle of the crayfish. Tension responses were first recorded when the cell was depolarized to about -60mV. Contractile tension was found to increase with both the magnitude and duration of the depolarization. Transmembrane and internal currents were only effective in producing tension to the extent that they decreased the potential difference across the cell membrane. Inhibition of the electrically induced contraction by gamma aminobutyric acid can be explained solely on the basis of the decrease in membrane resistance produced by this compound. Manganese 'uncoupled' the relation between depolarization and contraction without diminishing the 'excitability' of the membrane. (Supported by Grant No. 2G-153 and Fellowship No. GF-7925 Natl. Insts. of Health, PHS.)

ENDOCRINOLOGY
Bausch and Lomb Lecture Hall

IN SITU STUDY OF FATTY ACID RELEASE FROM ADIPOSE TISSUE. C. W. Nash*, R. L. Smith*, R. P. Maickel*, and R. Paoletti*. Natl. Insts. of Health, Bethesda, Md.

Studies from this laboratory have shown that adipose tissue contains significant amounts of norepinephrine (NE) (0.15 γ/gm). To elucidate further the role of NE in mobilization of fatty acids a technique has been developed to study the effect of drugs on fatty acid release from adipose tissue in situ. The vein from the adipose tissue of the dog's spleen suspensory membrane was cannulated to remove blood samples and measure blood flow. Increased free fatty acid (FFA) release was elicited by electrical stimulation of the sectioned distal end of the splenic artery nerve plexus (4 volts at 16 per second). FFA output was calculated from the plasma level and flow rate. The increased output of FFA after nerve stimulation was prevented by pretreatment with an adrenergic blocking agent (dibenamine)or by reserpine which depletes the NE from the nerve endings. NE stimulated the release of FFA if applied locally or injected intravenously into normal or reserpinized animals.

THE PHYSIOLOGICAL ROLE OF NOREPINEPHRINE IN LIPID MOBILIZATION FROM ADIPOSE TISSUE. R. P. Maickel*, R. Paoletti*, R. L. Smith*, and B. B. Brodie. Natl. Insts. of Health, Bethesda, Md.

Numerous studies have suggested that catecholamines have a role in the mobilization of free fatty acids (FFA) from adipose tissue. We have identified norepinephrine in adipose tissue of rats, dogs, and rabbits, and modified the spectrofluorimetric assay method of Shore and Olin to permit its accurate assay. The level of the amine in normal adipose tissue was found to range from 0.12-0.15 μgm/gm, and was lowered by reserpine in rat to < 0.03 μgm/gm. In normal rats, the administration of depot ACTH elicited a marked rise in plasma FFA and a significant deposition of liver triglycerides. Pretreatment of animals with reserpine prevented these responses. However, if norepinephrine was administered and then ACTH to the reserpinized animals, the rise in plasma FFA and liver triglycerides was again observed. These results suggest a vital role for norepinephrine in fatty acid mobilization from adipose tissue.

FURTHER STUDIES ON PLASMA LIPID MOBILIZER. James A. Miller* and Joseph Seifter. Wyeth Laboratories, Inc., Basic Medical Sciences Research Division, Radnor, Pa.

Lipid Mobilizer (LM) has been reported by Seifter and Baeder to be a low molecular weight, dialysable peptide appearing in mammalian plasma following cortisone administration, exposure to a variety of stresses, and starvation. Similar physiologically active material was also obtained from hog pituitary. This lipid mobilizer differs from Rudman's purified protein-peptide "Fraction H" since pepsin digestion is required to release a dialysable and active material. Plasma samples from dog, rabbit, and baboon following administration of phenylhydrazine, cortisone and other glucocorticoids have been subjected to dialysis, liquid and chromatographic fractionation procedures. The effect of these preparations on plasma free fatty acids (FFA), free and total cholesterol, esterified and total fatty acids and lipid phosphorus in the rabbit will be discussed.

EFFECT OF EPINEPHRINE ON ACTH RELEASE IN HUMANS. Joan Vernikos-Danellis* and Bernard H. Marks. Ohio State University College of Med., Columbus, Ohio.

This study attempts to define the temporal characteristics of ACTH release in normal human subjects following an acute stress. The standard stress utilized was an intravenous infusion of 0.25 or 0.50 μg/kg of epinephrine hydrochloride delivered in one minute. Control and post-infusion blood samples were assayed for ACTH activity by measuring adrenal ascorbic acid depletion in cortisol-blocked rats. Curves of ACTH release in male and female subjects both showed a peak at 2.5 minutes following the onset of the epinephrine infusion. The release of ACTH was significantly greater in females with the 0.50 μg/kg dose of epinephrine. Saline-injected humans showed no significant ACTH release. Epinephrine injected assay rats showed no significant adrenal ascorbic acid depletion. Dose-response curves for epinephrine vs. ACTH release for males and females will be presented. This test may be useful as an indication of anterior pituitary functional capacity. (Supported by grant A-5110 from The National Institutes of Health.)

PHARMACOLOGY OF BONE: GLYCOGENOLYTIC ACTION OF EPINEPHRINE. Alexander D. Kenny. Department of Pharmacology, West Virginia University Medical Center, Morgantown, West Virginia.

The calvaria were removed from 4-day old mice 1 hour after subcutaneous injection of epinephrine or saline; either the glycogen content or the *in vitro* aerobic and anaerobic lactic acid production in Krebs-Ringer-bicarbonate-glucose medium was measured.

Epinephrine Dose, mg/kg	Bone Glycogen mg/g	% fall	Lactic Acid Produced μmoles/ g/hr O_2	N_2	% increase O_2	N_2
0	2.3		7.8	17.6		
0.3	-		11.7	23.2	50	32
1.0	1.5	35	15.6	24.3	100	38

Epinephrine depleted the glycogen and increased the lactic acid production in mouse calvaria, indicating a glycogenolytic action on bone similar to this action on other tissues. The fact that epinephrine can increase the aerobic production of lactic acid raises the question of the specificity of a similar effect reported by Borle *et al.* (J.Biol.Chem., 235, 1211, 1960) with parathyroid hormone in metaphyseal bone. (Supported by a grant from NIH, A4276).

INHIBITION OF THE RESERPINE-INDUCED ACTH HYPERSECRETION WITH A MONOAMINE OXIDASE INHIBITOR (N-methyl-N-benzyl-propynylamine). R. Martel* and R. P. Maickel*. Natl. Insts. of Health, Bethesda, Md.

Previous studies have shown that reserpine (0.5 to 5 mg/kg i.v.) induces a marked hypersecretion of ACTH in rats as measured by decreased adrenal ascorbic acid and increased plasma corticosterone and liver tryptophan pyrrolase (TPO) (Brodie, B. B., *et al.*, Proc. 4th Int. Neurochem. Sym., Varenna, Italy, 1960, in press). It was suggested that this effect might be related to changes in brain serotonin levels. In the present work, rats were pretreated with N-methyl-N-benzyl-propynylamine (MO 911), and then given reserpine. Since the activity of brain monoamine oxidase was blocked, the amines released by reserpine were not metabolized and levels of NE and 5HT remained above normal. No hypersecretion of ACTH occurred. The antagonistic effect of MO 911 appears to be specific for reserpine; the MAO inhibitor does not prevent the adrenocortical response to ACTH, chlorpromazine or cold exposure. The results suggest that the hypothalamus-pituitary-adrenocortical system is not stimulated through reserpine *per se* but through an action on brain amines. Reserpine-induced ACTH hypersecretion will be discussed in relation to other central actions of the alkaloid.

EFFECT OF DRUGS ON INTESTINAL RELEASE OF STIMULANT ACIDIC LIPIDS IN RELATION TO EFFECT ON MOTILITY IN VITRO. Grace W. Cray. Marquette Univ. School of Medicine, Milwaukee, Wis.

Following the demonstration that lipid-soluble acids which stimulate gut motility are selectively depleted from the wall of the bowel under conditions of experimental obstruction ileus, a study was made of the influence of various drugs upon the amount of these stimulant acidic lipids (SAL) which are released during one hour into Tyrode's solution from living rabbit intestine *in vitro*. The Tyrode's biodialysates were extracted for butanol-soluble acids, and the motility stimulant potencies of the resulting extracts were determined by bioassay. It was found that dibucaine (10^{-6} and 10^{-5} gm/ml) had little influence on amount of SAL released from intestine, though it blocked the *in vitro* motility stimulant effect of added SAL. $MgCl_2$ (0.01M) was also found to have little effect on SAL release from intestine, though it produced marked depression of motility *in vitro* which was not restored to normal by added SAL. By contrast, epinephrine (10^{-6}, 10^{-5}, and 10^{-4} gm/ml) produced a graded depression of SAL release from intestine. In most cases, epinephrine depression of motility was either overcome immediately, or else recovery was hastened, by added SAL.

STUDY OF THE HYPOGLYCEMIC EFFECT OF METHYLGLYOXAL-BIS-GUANYL-HYDRAZONE (CH_3-G). E. Mihich, C.L. Simpson-Englander* and A.I. Mulherin* Dept. of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, N. Y.

The toxic hypoglycemic effect of CH_3-G was first observed in rabbits during pre-clinical pharmacological studies of this anti-tumor agent (E. Mihich *et al.*, Cancer Research 20, 609, 1960). Initial clinical testing revealed that CH_3-G also causes severe hypoglycemia in man (W. Regelson and J.F. Holland, Cancer Chemotherapy Reports 11, 81, 1961). In both rabbits and rats the hypoglycemia induced by CH_3-G (70 to 100 mg/Kg, I.V.) becomes evident after depletion of liver glycogen. Glycogen levels are not significantly altered in muscle. In rabbits, administration of glucose (1 gm/Kg, I.V.) 2 to 4 times during 5 to 15 hours causes only transient reversal of the hypoglycemia and does not cause repletion of liver glycogen which remains as low as 0.02%. Blood lactic acid is increased under these conditions. Hyperglycemia following glucagon (250 μg/Kg, I.V.) or epinephrine (150 μg/Kg, S.C.) does not occur in rabbits treated with CH_3-G at a time when glycemia is not yet altered but liver glycogen is already lowered. Deposition of glycogen in liver following repeated administration of cortisone (50 mg/Kg, S.C.) is inhibited in animals treated with CH_3-G. Liver necrosis is evident in the hypoglycemic animals. Prevention of glycogen deposition in liver by CH_3-G may initiate the effects observed.

SPECIES DIFFERENCES WITH REGARD TO CERTAIN CORTICOSTEROID EFFECTS. J. F. Noble*, M. F. Mazzei* and L. A. Kanegis.* Lederle Laboratories, Pearl River, New York.

A series of experiments have been carried out to study the relative effects of a potent glucocorticoid on several different species. The purpose was to determine if a species was available which would be suitable for complementing rat and dog toxicity studies on promising new steroids and to provide a more "steroid resistant" species which would be suitable for exploring possible toxicity peculiar to substituted groupings of analogs of parent steroids. Triamcinolone acetonide was given subcutaneously at a daily dose of 10 mg./kg. The parameters followed were body weight, relative changes in plasma proteins and plasma and tissue glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase. The changes which occurred in these parameters were decreased body weight or body weight gain, increased plasma and tissue glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase, increased plasma alpha globulins, decreased plasma gamma globulins and slightly decreased plasma albumins. The species tested are listed in decreasing order of severity of the changes produced: rat, mouse, gerbil, dog, rabbit, and guinea pig. The degree of the changes varied from marked with the administration of as few as 4 doses to rats to little or no change after the administration of 18 doses to guinea pigs.

EFFECT OF ADRENAL STEROIDS ON CHEMICALLY INDUCED THIAMINE DEFICIENCY. E. Schwartz* and R. W. Kanthei. Dept. of Pharmacol., Jefferson Med. College, Philadelphia, Pa.

Adrenal corticoids have previously been found to modify dietary induced thiamine deficiency. In the present study we have investigated the effects of adrenal corticoids on the deficiency induced in mice on a thiamine free diet by oxythiamine and pyrithiamine. Mice were injected with a single dose of 1.25 mg of pyrithiamine and examined daily for the onset of neurologic symptoms. Oxythiamine was administered intraperitoneally at 1 mg/mouse/day until death occurred. Subcutaneous injection of DOCA (0.1 mg/day) or aldosterone (10 u/day) significantly delayed the onset of neurologic symptoms or the time of death in each group. Subcutaneously administered cortisone (2.5 mg/day) significantly shortened the death times in both groups, the pyrithiamine-treated animals dying without neurologic symptoms. Weight changes and food intake of each group were determined and will be presented. It is concluded that the mineralocorticoids, DOCA and aldosterone, exert a protective action on chemically induced thiamine deficiency and the glucocorticoid, cortisone, aggravates this condition.

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INHIBITORY EFFECT OF DEOXYCORTICOSTERONE (DOC) IN VIVO ON HEPATIC ALANINE TRANSAMINASE ACTIVITY. H. R. Harding*, F. Rosen* and C. A. Nichol. Dept. of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, N. Y.

Treatment of rats with cortisol or other glucocorticosteroids caused marked increases in the activity of hepatic alanine-α-ketoglutarate transaminase; a number of other steroids and hormones were inactive in this respect (Rosen, et al., Endocrinology 65:256, 1959). In contrast to the effect of cortisol, treatment with DOC (30 mg/Kg daily for 7 days) reduced alanine transaminase activity in liver to 30 per cent of the normal endogenous value. Treatment with DOC (50 mg/Kg) did not impair the enzyme response to cortisol treatment (10 mg/Kg). Adrenalectomy of adult rats caused a decrease in the activity of alanine transaminase but no further reduction in the level of this enzyme was observed upon treatment with DOC. Treatment with ACTH results in marked increases in alanine transaminase activity in intact and hypophysectomized rats, but not in adrenalectomized animals. The administration of DOC to hypophysectomized rats failed to lower alanine transaminase activity of liver. When DOC was administered simultaneously with ACTH to hypophysectomized animals, the response of liver alanine transaminase to ACTH was not altered. The inhibitory effect of DOC on alanine transaminase activity appears to be due to the suppression of ACTH release by the pituitary.

EFFECT OF PARENTERAL DPPD ON PARTURITION IN THE RAT. Steven Carson*, Norman Sonnen*, William Langan*, Richard Goldhamer*, Arthur Mackars*, and Bernard L. Oser. Food and Drug Research Laboratories, Inc., Maspeth, New York City.

Diphenylparaphenylenediamine (DPPD) fed to pregnant rats at 1.6% of the diet for a 10-day period, including days 17-20 of pregnancy, delays parturition in pregnant rats. Studies are being made to determine the time required to elicit a similar response by parenteral administration, and the crucial day or days. Administration daily, over a 96-hour dosage schedule (64 mg/kg, subcutaneous) delayed parturition for about 3 days if initiated on days 15, 16, 17, and 18, of gestation. Studies are in progress in which 72-, 48-, and 24-hour time periods are employed. Possible antihormonal action of DPPD is being investigated. Steroid levels in blood and urine samples obtained from DPPD-treated pregnant and non-pregnant rats are being assayed by gas-liquid chromatography. Other areas of study of the mode of action of DPPD include the effect on membrane (staircase phenomenon), and the relation to carbohydrate and/or fat metabolism.

KIDNEY AND ELECTROLYTES
Morey 321

EFFECT OF PILOCARPINE ON SODIUM AND POTASSIUM TRANSPORT IN KIDNEYS OF INTACT RATS AND IN KIDNEY SLICES. M. Kathleen Carter, Gerald R. Hemstreet* and James W. Reid.* Dept. of Pharmacology, Tulane University, School of Medicine, New Orleans, La.

Previous investigations (Carter and Greig, Fed. Proc., 14, 324, 1955) have demonstrated that acetylcholine decreased the uptake of potassium and increased the uptake of sodium in incubated kidney slices of rats. It has also been shown (Carter and Atkinson, Fed. Proc., 20, 412, 1961) that physostigmine but not neostigmine caused an increase in sodium and potassium excretion in intact hydrated rats. Atropine given simultaneously blocked the effects of physostigmine. In the present investigation pilocarpine nitrate (1 to 10 mg./kg.) administered intravenously to orally hydrated rats causes, during a urine collection period of 4 hours, an increase in sodium excretion (2 to 10 fold) and a slight increase in potassium excretion. Atropine (0.1 mg./kg.) blocks the effects of pilocarpine. Results of preliminary experiments using rat kidney cortex slices incubated in a Krebs bicarbonate medium containing alpha-ketoglutarate indicate that pilocarpine (1×10^{-4} and 1×10^{-5} M.) causes an effect on sodium and potassium uptake similar to that found with acetylcholine. (Supported by USPHS Grant RG-5247 and Senior Research Fellowship SF-15.)

RENAL TUBULAR TRANSPORT OF m and p NITROHIPPURIC ACIDS. P. K. Knoefel. Dept. of Pharmacology, University of Louisville, School of Medicine, Louisville, Kentucky.

It has recently been claimed that these substances are poorly transported by the renal tubule on the basis of their small accumulation by renal cortical slices in vitro. Experiments in dogs in which loading with $NaHCO_3$ gave increasing volume and pH of urine showed that the calculated rate of tubular excretory transport of these 2 substances also increased, to maximal values no less than those obtained with the corresponding amino compounds. It is concluded that these nitro and amino hippuric acids are equally well transported; that the former, having greater lipoid solubility than the latter, more readily undergo passive tubular reabsorption. It appears that the estimation of transport by slices in vitro may also be in error as a result of passive movement of the substance being studied. (Supported by U.S.P.H.S. Grant H-3639).

RENAL EXCRETION OF ORGANIC BASES. Jerry M. Smith*, Glenn T. Peake* and Lawrence Peters. Dept. of Pharmacology, Kansas Univ. Med. School, Kansas City, Kan.

The renal clearance of mecamylamine in dogs exceeds glomerular filtration rate (GFR) when the urine is acid but is below GFR when the urine is alkaline. Quinine clearance also varies inversely with urine pH. Until recently these phenomena were ascribed to pH-dependent, bidirectional, passive diffusion of the unionized form of these amines across tubular cells. On the other hand, "bases" such as mepiperphenidol (Darstine) and N^1-methylnicotinamide (NMN) are known to be actively excreted by the tubules via active transport, this excretion being susceptible to depression by a cyanine dye (#863). Inhibition of tubular excretion of NMN by mecamylamine and quinine in chickens, previously reported from this laboratory, suggested that active tubular excretion of these amines can also occur. This possibility is now supported by the findings that quinine and mecamylamine inhibit tubular excretion of NMN, and that cyanine #863 and Darstine decrease renal excretion of mecamylamine, in the dog. These observations, consistent with those reported by Torretti et al. at these meetings a year ago, support the concept of active tubular excretion of mecamylamine and quinine, with simultaneous pH-dependent back diffusion. (Supported by USPHS Grant #H-2377).

EFFECT OF PAPILLECTOMY ON THE PROCESS OF URINE CONCENTRATION IN THE GOLDEN HAMSTER. T. B. Miller*, S. Marshall*, and A. Farah. SUNY, Upstate Medical Center, Syracuse, N. Y.

The effect of surgical removal of the distal 3 mm of the renal papilla has been evaluated by subjecting control and experimental hamsters to various regimens producing hydration and dehydration. Three groups of animals were studied: 1) bilateral papillectomy, 2) unilateral papillectomy and nephrectomy and 3) normal controls. When placed in metabolism cages and given carrots alone (hydrating diet), pellets alone (dehydrating diet), and pellets and water ad lib (normal diet) the following was observed: no difference in urine volume or osmolality on carrots alone; during progressive dehydration the more marked the dehydration the greater the difference between control and papillectomized animals; on normal diet the operated hamsters consistently excreted twice the volume of a more dilute urine than the controls. Water loads were excreted more rapidly by the papillectomized groups. Simultaneous administration of a 6% oral water load and 100 milliunits of vasopressin i.m. showed that the ability of the papillectomized hamsters to respond to ADH was reduced. These results are consistent with the countercurrent hypothesis. (Supported by grants Nos. H-2835 and A-3847, USPHS, National Heart Institute and National Institute of Arthritis and Metabolic Diseases.)

THE MODE OF HYDRATION AS A FACTOR IN THE RENAL PHARMACOLOGICAL EFFECTS OF HYPOTENSIVE AGENTS. G. L. Wagle*, J.W.Russell,Jr.*, and A. J. Plummer. Research Dept., CIBA Pharmaceutical Products Inc., Summit, New Jersey

Mannitol, water or saline-induced diuresis in the unanesthetized dog assures a constant urine flow in renal function tests where inulin and PAH are used for the determination of the glomerular filtration rate (GFR) and renal plasma flow (RPF) respectively. Five % mannitol administered I.V. at 5-6 ml/min. gave a urine flow equal to the input. Water administered orally at 60 ml/kg produced a urine flow of 5-7 ml/min at 1 to 2 hrs. Saline administered at 3 ml/min I.V. resulted in a urine flow of 0.5 to 2.0 ml/min. When the oral water regime is added to the saline infusion, the urine flow may reach 8-10 ml/min. Reserpine administered to several species causes an antidiuresis with some retention of Na^+ and K^+ and no effect on GFR and RPF. We have found an increase in RPF after reserpine given in repeated small doses for 8 days and in large, single I.V. doses by all methods of hydration. Antidiuresis was noted only when oral water was used as the diuretic agent. Reserpine does not alter mannitol diuresis, but it potentiates saline diuresis. Reserpine and some of its analogues have been tested under the various types of hydration. The extent of diuresis, the Na^+ and K^+ excretion, the GFR and RPF have been determined.

RENAL PHARMACOLOGY OF AN ANTIHYPERTENSIVE DES-SULFAMYL BENZOTHIADIAZINE. R. M. Taylor,* R. M. Milton,* M. J. Powers* and M. M. Winbury. Dept. of Pharmacology, Schering Corp., Bloomfield, N. J.

Rubin et al. demonstrated that 3-methyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide (SRG 95213) reduces blood pressure (BP) in normo- and hypertensive animals. In the present study 1 to 5 mg/kg i.v. in anesthetized dogs induced a moderate fall in BP but had little or no effect on urine and electrolyte excretion. Higher doses caused a prolonged reduction in urine, Na and Cl output. This reduction was not associated with any change in GFR but ERPF (PAH clearance) generally declined. Free water clearance was also diminished during water diuresis in unanesthetized dogs. In spite of these acute renal effects, 5 and 20 mg/kg/day for 21 days p.o. did not modify urine and electrolyte excretion, plasma electrolytes or body weight. In normal and ADX rats SRG 95213 suppressed excretion of a saline load at doses $\geq$ 10 mg/kg p.o. even though little or no reduction in BP was observed. This action was reversed by benzothiadiazine diuretics and carbonic anhydrase inhibitors but not by xanthine diuretics. The lack of diuretic activity observed with this agent suggests that a separation of the antihypertensive and renal actions associated with 7-sulfamyl benzothiadiazines may have been achieved.

RENAL CLEARANCE OF POLYTHIAZIDE. A. Scriabine*, E. C. Schreiber* and M. Yu*. Chas. Pfizer & Co., Inc., Groton, Conn.

Polythiazide, 2-methyl-3-(β,β,β-trifluoroethyl-thiomethyl)-6-chloro-7-sulfamyl-3,4 dihydro-1,2,4 benzothiadiazine, 1, 1 dioxide is a new orally effective diuretic. In the previous studies, we demonstrated long duration of action (24 hours) and high potency of this drug. Recent studies were concerned with the renal excretion of polythiazide. The drug was labeled in the 2-position with C^{14}. The clearance of the labeled drug was studied in anesthetized dogs infused with isotonic sodium chloride or sodium bicarbonate solution. The ratio $\frac{\text{drug clearance}}{\text{creatinine clearance}}$ was found to be considerably lower for polythiazide than for other thiazide diuretics. The intravenous administration of probenecid decreased the clearance ratio indicating that polythiazide is secreted by the renal tubuli. A series of stop-flow experiments was performed with C^{14} labeled polythiazide. The $\frac{U/P\ Drug}{U/P\ Creatinine}$ ratio was found to be considerably lower in the lower portion of the proximal and in the upper portion of the distal tubuli than in free flow control samples. The long duration of polythiazide action is apparently determined by its low renal clearance.

EVALUATION OF THERAPEUTIC EFFICIENCY OF DIURETIC DRUGS. Duncan E. Hutcheon and D. K. Rowland.* Dept. of Pharmacology and Medicine, Seton Hall College of Medicine and Dentistry, Jersey City, N. J.

Using a standard factorial design the relative potency of hydrochlorothiazide and quinethazone (2-ethyl-7-chloro-6-sulfamyl-1,2-dihydro-4-quinazolone) was determined in patients with congestive heart failure. The drugs were given at doses of 50 and 100 mg per day for one week at each dosage level. One week of placebo therapy separated the weeks of diuretic therapy. Weight loss was used as a measure of diuretic response and plasma electrolytes were measured at weekly intervals. The relative activity of quinethazone to hydrochlorothiazide on a mg basis was estimated to be 68%. In addition from an analysis of the dose-response relationships the therapeutic efficiency of hydrochlorothiazide was found to be similar to that of quinethazone. The s/b ratio in this bioassay was 0.17. (Supported by the United States Public Health Service Grant H-5240).

TUESDAY MORNING

KIDNEY AND ELECTROLYTES

COMPARISON OF HYDROCHLOROTHIAZIDE AND QUINETHAZONE IN THE TREATMENT OF NON-AMBULATORY PATIENTS WITH CONGESTIVE HEART FAILURE. R. W. Payne, J. R. E. Valadares* and R. R. Cole.* Univ. of Okla. School of Med., Okla. City, Okla.

The diuretic properties of hydrochlorothiazide, an aromatic disulfonamide, were compared with those of quinethazone (2-ethyl-7-chloro-6-sulfamyl-1,2-dihydro-4-quinazolone), an aromatic monosulfonamide, in 14 bedfast digitalized patients with chronic congestive heart failure. On the basis of urinary and serum Na, K and Cl changes the drugs were equally effective when daily doses of 50 mg. of hydrochlorothiazide were compared with 100 mg. of quinethazone. Electrolyte changes were more prominent than effects on urinary volume. All patients were maintained grossly edema-free with both compounds. While the serum BUN tended to initial slight elevation in the group, no further increase was provoked by either drug. Serum uric acid concentrations were elevated by the agents in 9 of the patients - most marked in one patient with associated gout. Both agents exhibited a comparable mild antihypertensive effect. It is concluded that although both of the diuretic agents show similar qualitative effects, quinethazone is half as potent as hydrochlorothiazide on a mg. basis.

FURTHER LABORATORY STUDIES ON TRIAMTERENE, SK&F 8542. V. D. Wiebelhaus*, J. Weinstock*, F. T. Brennan*, G. Sosnowski*, T. Larsen* and K. Gahagan*. Smith Kline & French Labs., Philadelphia 1, Pa.

Triamterene, SK&F 8542 (2,4,7-triamino-6-phenyl pteridine) antagonizes the effects of aldosterone on both Na^+ and K^+ in the rat and the dog. Triamterene reduces the kaliuretic effects of chlorothiazide in dogs. These observations suggest that the pteridine influences the renal secretion of K^+. This K^+ effect is much more pronounced in the acidotic than in the alkalotic dog. When SK&F 8542 is administered to dogs receiving infusions of KCl, natruresis ensues but there is no evidence of an effect on the excretion of K^+ under these circumstances. This distinguishes the natruresis of the pteridine from that of the cardiac glycosides which do not produce natruresis under these conditions. It also suggests that when plasma levels and/or filtered loads of K^+ are elevated the K^+ effect of the pteridine is essentially nil, suggesting a self-limiting phenomenon. Given to an adrenalectomized dog supported on a high sodium diet but with no steroidal supplements, SK&F 8542 consistently increased sodium outputs, the responses ranging up to 53 per cent increase. While triamterene certainly antagonizes the effects of aldosterone on both Na^+ and K^+ it may be more properly designated as an inhibitor of the renal transfer of Na^+ and K^+, possibly with a distal site of action.

SOME ACID-BASE EFFECTS OF 5,5'-DIMETHYL-2,4-OXAZOLIDINEDIONE (DMO) IN RATS. C. Dean Withrow* and Dixon M. Woodbury. Dept. of Pharmacology, University of Utah, Salt Lake City.

Intraperitoneal administration of 500 mg/kg of DMO to adult Sprague-Dawley rats caused marked changes in tissue and plasma acid-base parameters. Plasma total carbon dioxide concentration was reduced from approximately 23 to 16 mM/L after drug treatment. Decreases of about 3 mM/kg wet weight in total carbon dioxide content of both skeletal muscle and cerebral cortex were observed in the same animals. DMO effects were maximal in approximately 3 hours and had waned in 5 to 6 hours. Treatment of rats with 100 mg/kg DMO also resulted in significant but smaller changes in plasma and tissue carbon dioxide values. These experiments indicate that DMO is not an inert compound insofar as acid-base metabolism is concerned. The use of this drug to estimate cell pH in rat tissues must be cautiously applied if meaningful values for cellular hydrogen ion concentrations are to be obtained. (Supported by grants 2G-153 and B-381, N.I.H., and by National Neurological Research Foundation.)

PSYCHOPHARMACOLOGY I
Dewey 114

ANTAGONISM OF LYSERGIC ACID DIETHYLAMIDE (LSD)-INDUCED HYPERTHERMIA. John T. Elder* and M. Kent Shellenberger*. Dept. of Pharmacology, University of Washington, Seattle 5, Wash.

Various agents have been used in attempts to prevent the pyretogenic response to LSD, 50mcg/kg I.V. as a means of determining the mechanism by which it occurs. Male rabbits were used and temperatures were recorded every 30 min. for 2 hours before and during 5 hours after LSD. Hexamethonium, 10 mg/kg I.V. 30 min. before LSD did not affect the temperature rise. Phenoxybenzamine, 10 mg/kg I.V., 60 min. prior to LSD not only abolished the rise in temperature but reduced it below control levels. The same dose given 23 hours prior to LSD produced significant reduction in the response also. Reserpine, 2 mg/kg I.V. immediately prior to LSD produced a potentiation of the LSD response. Guanethidine, 10 mg/kg I.V. 18 hours before LSD caused significant attenuation of the response. Both reserpine and guanethidine were given on a time schedule intended to produce maximal amine depletion at about the time the peak pyretogenic response to a subsequent dose of LSD occurred. The difference in the effects of these two agents may be due to the relative speed of release of amines; reserpine producing a much more rapid release than guanethidine. Also to be considered are release of peripheral and central catecholamines and serotonin.

(Supported by Initiative 171 Funds, State of Washington)

DRINKING INDUCED BY CHOLINERGIC STIMULATION OF HYPOTHALAMUS IS A MUSCARINIC, NOT NICOTINIC, ACTION. Larry Stein* and Joseph Seifter. Basic Medical Sciences Research Division, Wyeth Laboratories, Radnor, Pa.

Grossman (Science 132:301, 1960) has reported that eating or drinking can be elicited by the direct application of crystalline substances into the lateral hypothalamus of the rat. Adrenergic substances (norepinephrine and epinephrine) selectively induced eating, and cholinergic substances (carbachol, acetylcholine capped by physostigmine) selectively induced drinking. We have confirmed and extended the cholinergic findings. Minute quantities (1-5 μg) of crystalline compounds were introduced into the brains of 28 rats through permanently indwelling cannulae. Muscarine had an effect equal to carbachol, producing strong drinking within 5-10 minutes that persisted with variable intensity for almost an hour. Nicotine had the same, small "non-specific" effect as sodium chloride -- about twice as much as no-drug controls, but only 20% of the effect of carbachol or muscarine. (Potassium chloride and sucrose had no effect). The effects of carbachol and muscarine were largely blocked by prior application of atropine. These findings suggest that cholinergically-induced drinking is a muscarinic, not nicotinic, action. We confirmed also that noradrenaline elicits eating, but our adrenergic effects have been smaller and less reliable than the cholinergic ones.

A SYSTEMATIC EVALUATION OF THE EFFECTS OF MONO-URETHANES, DI-URETHANES AND BARBITURATES ON EXPERIMENTALLY INDUCED CONFLICT. Irving Geller* and Joseph Seifter. Wyeth Institute for Medical Research, Radnor, Penna.

A separation of some aliphatic hypnotics from phenothiazines based upon their effects upon experimentally induced "conflict" has recently been demonstrated (Geller and Seifter: Psychopharmacologia 1: 482, 1960). The conflict behavior was induced in the presence of a tone stimulus by simultaneously rewarding with food and punishing with shock lever responses of hungry rats. Meprobamate and barbiturates, in contrast to phenothiazines, attenuated the suppression of responding which occurred during the tones as a result of the above procedure. Periods between tones when rats worked only for food permitted control observations for non-specific behavioral depression (side-effects). The present study is a survey of structurally related compounds known to give qualitatively similar effects in the "conflict" test. Our intent was to determine the degree of conflict attenuation for each drug relative to the side effect of non-specific depression. Meprobamate, a di-urethane, produced the maximum attenuation of conflict at a dose which produced a minimum of side effects. The mono-urethanes, hedonal, emylcamate, and urethan, produced the least amount of conflict attenuation and intermediate effects were produced by pentobarbital and phenobarbital.

LAIII, A NEW PSYCHOTROPIC DRUG. R.F. Banziger.* Department of Pharmacology, Hoffmann-La Roche, Inc., Nutley 10, New Jersey.

LAIII (7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepine-2 (1H)-one) is considerably more active than chlordiazepoxide as a tranquilizer and anticonvulsant. Pentobarbital Na and hexobarbital Na produce excitement in dogs during induction of anesthesia when administered intravenously. Preanesthetic treatment of the dogs with LAIII completely abolishes this excitement. The anesthetic doses of the barbiturates in dogs and cats are reduced appreciably. LAIII produces hypnosis in mice when administered orally simultaneously with subhypnotic doses of 95% ethanol. Chlordiazepoxide and meprobamate potentiate 95% ethanol to a lesser degree. LAIII, chlordiazepoxide and meprobamate do not influence 95% ethanol oral toxicity in mice acutely or after subchronic administration of the compounds. LAIII effects on other excitement-producing drugs will be discussed. Valium ™ is the trade name for LAIII.

SOME EFFECTS OF SCOPOLAMINE, ATROPINE AND AMPHETAMINE IN THREE BEHAVIORAL SITUATIONS. Peter L. Carlton*. The Squibb Institute for Medical Research, New Brunswick, New Jersey.

The effects of scopolamine hydrobromide (0.3 - 0.6 mg/kg), atropine sulfate (2.0 - 8.0 mg/kg), and d-amphetamine sulfate (0.25 - 2.0 mg/kg) were studied in operant-behavior situations in which food-deprived rats were differentially reinforced with food for (a) responding at a rate no greater than 1 response/18 seconds, (b) for alternating their responses between two manipulanda, (c) responding to only one of five available manipulanda. In situation (c) the "correct" manipulandum was randomly varied so that the animal was required to learn, on a trial and error basis, which of the five produced reinforcement. All three drugs produced marked increases in response rate in (a); amphetamine was more potent than atropine and equally or slightly less potent than scopolamine. In (b), scopolamine drastically disrupted the rats' tendency to alternate and was clearly the most potent; amphetamine was more potent than atropine but the potency-difference was less than in (a). Preliminary data from (c) indicate that amphetamine and atropine had only moderate effects, whereas scopolamine produced a profound reduction in the animals' ability to learn the "correct" response.

INTERACTION EFFECTS OF IMIPRAMINE AND D-AMPHETAMINE ON NON-DISCRIMINATED AVOIDANCE. Albert Weissman*. Chas. Pfizer & Co., Inc., Groton, Conn.

Sixteen rats were stabilized on a non-discriminated avoidance task; the interacting effects of imipramine and d-amphetamine were then investigated. Imipramine (10 mg/kg I.P.) augmented and prolonged the stimulant effect of d-amphetamine (1 mg/kg I.P.). This effect was not a simple magnification of the effect of d-amphetamine given alone. A behavioral index (shocks received in control sessions) correlated negatively with the stimulant effect of imipramine plus d-amphetamine. Pretreatment time with imipramine (10 mg/kg I.P.) altered the d-amphetamine potentiation effect; the longer the pretreatment time, up to 24 hours, the faster and more pronounced the potentiation. Ten mg/kg I.P. of imipramine was more effective than 5 mg/kg I.P. in potentiating a simultaneous dose (1 mg/kg I.P.) of d-amphetamine. Twenty and 40 mg/kg I.P. of imipramine produced initial antagonistic effects on d-amphetamine stimulation. Amitriptyline (10 mg/kg I.P.) qualitatively resembled imipramine, but its effect was more rapid in onset and shorter lived. Chlorpromazine (2.5 mg/kg I.P.) antagonized the stimulant effect of d-amphetamine. The results are consistent with a recent proposal (Sulser, F., Watts, J. S., and Brodie, B. B.: Fed. Proc. 20: 321, 1961.) that the stimulant effect of imipramine is mediated by a metabolite.

THE EFFECT OF PHENELZINE ON THE PHARMACOLOGY AND TOXICOLOGY OF VARIOUS DRUGS. John Shanaman,* Jane Frances Emele,* V. Carolyn Scott,* W. E.Rowe,* M. R. Warren and C. C. Scott. Dept. of Pharmacology, Warner-Lambert Res. Inst., Morris Plains, N. J.

The effect of acute and chronic administration of phenelzine on the toxicity and pharmacology of various drugs in mice was studied. Chronic administration of phenelzine did not alter the LD_{50} of morphine sulfate, diphenylhydantoin sodium acetylsalicylic acid, ethyl alcohol, histamine phosphate, chlorpromazine, succinylcholine chloride, metrazol, demerol hydrochloride, imipramine, and pentobarbital sodium. The toxicity of norepinephrine bitartrate, hexamethonium chloride, ephedrine hydrochloride and serotonin creatinine sulfate was increased. Chronic administration of phenelzine 1) did not effect the anticonvulsant activity of phenobarbital sodium, 2) potentiated the analgesic activity of morphine sulfate, 3) markedly increased the analgesic activity of aspirin and 4) increased evipal-induced sleeping time. The effects of phenelzine on the anticonvulsant activity of diphenylhydantoin sodium, the CD_{50} of metrazol and the analgesic activity of meperidine was also studied.

COMPARISON OF TRANQUILIZERS BY HUMAN BIOASSAY T. Bodi§ P.E.Siegler§ J. W.Slap*, R.Khorsandian*, J.H. Nodine* Hahnemann Med. Coll. & Hosp. Philadelphia, Pa.

This study describes further experiences with the human bioassay of tranquilizers. Comparison of animal and human bioassay of 4 butyrophenones reported previously (The Pharmacologist 2:64, Fall, 1960) suggested a relative correlation in the transposition of data from animals to man. A comparative double blind, double dose bioassay of chlordiazepoxide, meprobamate, fluphenazine and placebo was carried out in 7 randomized groups of 50 patients each treated for 6 weeks. The effective doses resulted in clinically satisfactory responses as follows: fluphenazine 63, meprobamate 60, chlordiazepoxide 58 and placebo 33% of patients. Structured interview of patients revealed highly suggestive improvement on chlordiazepoxide 80 mg/day and meprobamate 800-1600 mg/day. In Digit Symbol Substitution, Figure Drawings, Sentence Completion Test, Pursuit Rotor Test and Reaction Time Test showed suggestive or significant improvement at lower doses and some decreased scores with high doses.

TUESDAY MORNING

PSYCHOPHARMACOLOGY I

BIOCHEMICAL CORRELATES OF PHARMACOLOGIC ACTIVITY. H. Green*, R. W. Erickson* and J. L. Sawyer*. Smith Kline & French Labs., Philadelphia 1, Pa.

The ability of the potent monoamine oxidase inhibitor, tranylcypromine (trans 2-phenylcyclopropylamine), to arouse rats from reserpine-induced sedation was closely correlated with restoration of the capacity of the brain to accumulate serotonin (5HT) at a normal rate, without any significant increase in the brain norepinephrine (NE) concentration. The marked excitation elicited following the injection of reserpine to rats pretreated with tranylcypromine was associated with a markedly elevated brain 5HT concentration in the presence of normal NE level. The failure of iproniazid (1-isonicotinyl-2-isopropylhydrazine) to reverse the sedation was accompanied by a marked decrease in the ability of the inhibitor to raise the brain 5HT concentration. The ability of reserpine to elicit increased motor activity of rats pretreated with iproniazid was dependent upon the pretreatment time of iproniazid, and was associated with markedly elevated levels of brain 5HT. Differential centrifugation studies of sucrose homogenates of rat brains indicated that the foregoing pharmacologic responses were not related to any selective increase in the free form of 5HT.

TUESDAY AFTERNOON

TOXICOLOGY
Lattimore 109

EFFECT OF THIORIDAZINE ON CANINE HEPATIC BLOOD FLOW. Gabriel L. Plaa, Eileen T. Eckhardt*, and Thomas D. Darby. Dept. of Pharmacology, Tulane Univ. School of Medicine, New Orleans, La.

The acute effects of thioridazine (Mellaril) on portal hemodynamics were studied in dogs anesthetized with pentobarbital. Blood pressure measurements were made using Statham transducers. Blood flow was determined with a square-wave electromagnetic flowmeter, and myocardial isometric tension with a strain gauge arch. Intraportal injections of doses as low as 2 mg/kg produced substantial rises in portal pressure and marked decreases in portal flow. When administered intravenously, 2, 4 and 8 mg/kg doses of this phenothiazine caused a biphasic response, with the portal flow changes resembling those seen with the intraportal route. The duration of this effect was dose-dependent but usually lasted longer than 20 minutes. This effect was preceded by a transient increase in portal flow, thoracic inferior vena caval flow, abdominal vena caval blood pressure, myocardial isometric tension, and cardiac output; portal pressure, aortic blood pressure, and right atrial pressure decreased. This effect usually lasted from 0.5 to 1.5 minutes. Vagotomy and preganglionic sympathetic blockade with procaine prevented the initial changes but not the persistent decrease in portal flow. Whenever portal flow decreased, liver ischemia was noted by gross observation, and upon cutting no bleeding was observed.

EFFECT OF PHENOTHIAZINES ON HEPATIC BLOOD FLOW IN THE MOUSE. Eileen T. Eckhardt* and Gabriel L. Plaa. Dept. of Pharmacology Tulane Univ. School of Medicine, New Orleans, La.

A dye-disappearance method has been devised for indirectly estimating hepatic blood flow in mice. From a series of disappearance curves, the optimal conditions were found to be a 150 mg/kg, i.v., dose of bromsulphalein, followed in 30 minutes by cardiac puncture for blood sampling. The method was assessed by using ephedrine, methoxamine, dibenzyline, phentolamine and barbital. Orally, chlorpromazine (6.2 mg/kg), thioridazine (10 mg/kg) and mercaptothiazinyl (78 mg/kg) were all found to decrease hepatic blood flow, in that they caused increased retention of the dye. This effect reached its maximum in about 2 hours and persisted for 4-8 hrs. Dose-response curves were established for each phenothiazine. Liver ischemia could be grossly observed, particularly with chlorpromazine. Acutely, qualitatively similar effects occurred after intravenous administration. However the dosage necessary to elicit the effect by this route was surprisingly higher than that required orally. From a 2-week oral chronic study, it was found that no cumulative effect occurred, but some degree of tolerance did develop to a subsequent acute challenging dose. Tolerance also developed to the hypothermic response elicited by these compounds. (Supported in part by USPHS grant A-3438 and a grant from Sandoz Pharmaceuticals.)

EFFECT OF ETHANOL INTOXICATION ON $CHCl_3$-INDUCED LIVER DAMAGE. S. David Kutob* and Gabriel L. Plaa. Dept. of Pharmacology, Tulane Univ. School of Medicine, New Orleans, La.

Individuals recovering from acute ethanol intoxication seem more susceptible to the liver-damaging properties of halogenated hydrocarbons than do non-intoxicated individuals. This phenomenon has been studied on Swiss albino mice, subjected to a single intoxicating dose of ethanol (5 gm/kg, p.o.), and then challenged with a single minimally hepatotoxic dose of $CHCl_3$ (0.08 ml/kg, s.c.), 12, 15 or 24 hours later. Liver damage was assessed by pentobarbital sleeping time, bromsulphalein retention, liver succinic dehydrogenase activity, and by histopathology. The incidence of liver damage in the groups subjected to $CHCl_3$ 12 or 15 hours after the ethanol pretreatment was found to be significantly increased. The most pronounced effect occurred when the ethanol preceded the $CHCl_3$ by 12 hours. Liver $CHCl_3$ concentrations were significantly elevated in mice pretreated with ethanol. By 6 hours no ethanol could be detected in the mice; however, liver triglycerides were significantly elevated after ethanol for a period of 21 hours. The data are interpreted to indicate that the increase in susceptibility to $CHCl_3$-induced liver damage is most likely due to an increased partition of $CHCl_3$ into the liver, because of the elevated lipid content induced by the ethanol. (Supported by USPHS grant A-3438 and a Licensed Beverage Industries, Inc. grant.)

EFFECTS OF DILUTED AUTO-EXHAUST ON PULMONARY FUNCTION OF GUINEA PIGS. S. D. Murphy*, J. K. Leng*, and C. E. Ulrich*. Div. of Air Pollution, USPHS, Robert A. Taft Sanitary Engineering Center, Cincinnati, Ohio.

A method (Mead, J. App. Physiol., 15, 325, 1960) for measuring pulmonary function in intact, unanesthetized guinea pigs was modified to permit repetitive, serial measurements on five animals in a single experiment. This method was applied to studies of the effect of exposure to diluted auto-exhaust produced under controlled conditions of engine operation and irradiation simulating solar spectrum and intensity. Tidal volume, respiratory rate, total pulmonary flow resistance and cardiac rate were measured at fifteen minute intervals before, during and after exposure to polluted atmospheres. Total expiratory flow resistance and tidal volume increased an average of 133% and 18% respectively and respiratory rate decreased by 26% when guinea pigs were exposed to irradiated atmospheres containing 1 part exhaust to 150 parts clean air. Exposure to irradiated air-exhaust mixtures at a ratio of 360:1 caused similar but lesser effects. Changes observed during a single exhaust-exposure were rapidly reversible following removal from the contaminated atmosphere. Nonirradiated exhaust mixtures at comparable dilution ratios produced little or no effect. Thus, dynamic, pulmonary function measurements distinguish between the toxic potential of irradiated and non-irradiated exhausts.

TOXICITY AND EXCRETION OF EPSILON AMINO CAPROIC ACID. D. W. Hallesy*, C. H. Hine* and N. Yuda.* Lederle Laboratories, Pearl River, New York.

As part of the safety evaluation studies on epsilon amino caproic acid (E.A.C.A.); acute and chronic toxicity studies were carried out in rats and dogs. No deaths were seen in rats following single oral doses as high as 10 g/kg. The acute intraperitoneal LD_{50} for rats was calculated as 7.0 g/kg while the acute intravenous LD_{50} of E.A.C.A. for rats was estimated to be 3.3 g/kg. When E.A.C.A. was fed to rats at dietary levels as high as 1%, for 1 month, no clinical signs of drug induced toxicity were observed. Rats fed diets containing 5 or 15% E.A.C.A. for 1 month, were hyperexcitable and had a decreased food intake and body weight gain. A dog receiving an intravenous infusion of E.A.C.A. developed tonic convulsions when 2.15 g/kg had been administered. This dog expired 5 hours later. No changes have been seen in the body weights, or clinical chemistry of dogs receiving oral doses as high as 1 g/kg of E.A.C.A. per day, for 5 months. Studies on the excretion of tritium labeled E.A.C.A. in dogs indicate that approximately 90% of the tritium label is recovered in the urine within 24 hours. Paper chromatography has shown that the majority of this is unchanged E.A.C.A. with a small amount appearing as a metabolite which appears to be adipic acid.

A STUDY OF THE TOXIC EFFECTS OF CINNAMON OIL. M.F. Powers*, T.D. Darby, and F.W. Schueler. Dept. of Pharmacology, Tulane U., Sch. of Med. New Orleans, La.

Swiss Albino male mice were used for acute toxicity study. Adult mongrel dogs anesthetized with pentobarbital were used for respiratory and cardiovascular studies. Polyethylene catheters attached to Statham transducers were used to measure blood pressures. Isometric tension and muscle segment length of a section of ventricular muscle were measured in-situ by the strain gauge lever system method. A Sanborn 154 Polyviso was used for amplification and recording the measurements. The intraperitoneal LD_{50} (Litchfield and Wilcoxan) was: cinnamon oil 0.5 gms/kg; cinnamaldehyde 0.46 gms/kg; sodium cinnamate 2.0 gms/kg; and cinnamyl acetate 1.2 gms/kg. Cinnamon oil, 100 mg/kg, caused an increase in isometric systolic tension, respiratory stimulation, hypotension and pulmonary edema. Death occurred within two hours. Similar results were obtained with cinnamaldehyde. Atropine and hexamethonium limited the pulmonary edema. The other compounds were less toxic in the dog.

TOXICOLOGICAL AND PATHOLOGICAL STUDIES WITH DIETHYLDITHIOCARBOMATE (DDC). Jean Scholler, D. E. Brown*, and E. K. Timmens*. Chas. Pfizer & Co., Inc., Maywood, New Jersey

Single lethal IP doses in rodents produced listlessness, dyspnea and impaired motor function of hind legs prior to death. Single lethal IV doses in dogs resulted in salivation, emesis and depression. No convulsions or delayed deaths were seen in either species. Single LD_{50} doses were approximately 1750, 1250 and 1000 mg/kg respectively for mice, rats and dogs. Subacute toxicity studies in rats revealed no remarkable toxic manifestations at lethal doses; the LD_{50} was 1000 mg/kg/day. Emesis, weight loss, weakness and anemia were noted in dogs receiving multiple IV doses. In dogs given single doses of 400 mg/kg or higher of DDC, and in dogs given repeated non-lethal doses, the pertinent findings were related to changes in the eye; dilatation and fixation of the pupils, loss of light reflex and either a progressive opacification of the vitreous humor or anteromedial retinal protrusion, with resultant blindness. Histopathological studies revealed a retinal detachment in the area of the tapetum lucidum of the choroid layer. These changes appeared to be species specific as they were not found in rats, cats, rabbits or monkey. They resembled similar changes seen in dogs treated with Dithizone, another chelating agent.

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CHRONIC ORAL TOXICITY OF OIL SWEET BIRCH (METHYL SALICYLATE). Elias W. Packman*, D. D. Abbott*, B. M. Wagner*, and Jos. W. E. Harrisson, LaWall and Harrisson Research Laboratories, Philadelphia 3, Penna.

A two year chronic toxicity or safety study employing natural Oil of Sweet Birch, U. S. P. XV, wherein weanling albino rats were used has shown no evidence of adverse effects. The test substance was included in the dry diet of the animals at concentrations of 700 and 2100 p. p. m. (0.07 and 0.21 per cent). Growth, survival, food usage, and general physical condition of the test animals was comparable with that of the control animals. Routine blood and urine studies were normal. Necropsy disclosed no adverse findings of significance, nor were such noted upon histologic study, in comparison with control animals. Fifty animals equally divided in regard to sex, and littermate distributed, comprised each of the test level groups and the control group. A smaller group of animals received "butter yellow" at a concentration of 0.06 per cent in the diet as a positive hepatic carcinogen.

CHRONIC ORAL TOXICITY OF OIL OF SASSAFRAS AND SAFROL. D. D. Abbott*, Elias W. Packman*, B. M. Wagner*, and Jos. W. E. Harrisson, LaWall and Harrisson Research Laboratories, Philadelphia 3, Penna.

Natural Oil of Sassafras (Southern) N. F. X, and Safrol were the test materials in a two year chronic toxicity study. Each of the test substances was fed at concentrations of 390 p. p. m. and 1170 p. p. m. in the dry diet. Routine blood and urine examinations were within normal limits. After twenty-two months representative animals from the high level were necropsied and the liver and kidneys examined microscopically. There was some evidence of kidney congestion but no liver tumors were observed grossly or histologically. However, at twenty-four months in an appreciable percentage of the animals, cellular changes in the liver, compatible with carcinoma were observed in all experimental groups. In addition, significant cellular changes were observed in the kidneys, adrenals, thyroid, pituitary, and testes or ovaries.

The marked contrast in tumor response of the liver at twenty-two and twenty-four months is indicative of a weak carcinogen which requires prolonged insult to a biologic system before manifesting cellular changes.

CHRONIC TOLERANCE STUDIES IN DOGS OF ANALGESIC RO 4-1778/1. R.E.Bagdon, C.Impellizzeri* and J. Courter*. Dept. of Pharmacology, Hoffmann-La Roche Inc., Nutley, N. J.

The analgesic properties of RO 4-1778/1, 1-(p-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were described by Brossi, et al. (Helvet. Chim. Acta. 43, 1459-1472, 1960); subsequent clinical investigations confirmed the analgesic activity of this tetrahydroisoquinoline derivative (Sadove, Ali and Schiffrin, Ill. State Med. J. 117, 425, 1960). Groups of 8 dogs were initially administered 40 mg/kg, 20 mg/kg and 10 mg/kg of RO 4-1778/1 orally, but the dose given to some dogs was gradually increased to 70 mg/kg; 6 months of treatment have been completed. Moderate side effects characterized by gastrointestinal disturbances were caused by 70 mg/kg but animals treated with lower doses exhibited a normal appearance. Laboratory findings, taken at frequent intervals, remained within normal limits. These included determinations of the hematocrit, hemoglobin, total and differential leukocytes, E.S.R., bromsulphalein retention, serum bilirubin, thymol turbidity, B.U.N., alkaline phosphatase, serum lactic dehydrogenase, serum isocitric dehydrogenase, SGO-T and SGP-T. These data are in agreement with results obtained in other investigations of RO 4-1778/1, indicating this analgesic to exert minimal untoward reactions.

TUESDAY AFTERNOON

TOXICOLOGY

ACID-BASE BALANCE DURING BARBITURATE POISONING. Lester C. Mark, Per Lous* and Ebbe Miltherg*. Columbia Univ.,New York and Bispebjerg Hosp., Copenhagen.

Acid-base balance after massive overdosage with barbital, phenobarbital, aprobarbital, amobarbital or pentobarbital, singly or in combination, was studied in 27 patients receiving physiologically supportive therapy without analeptics. Twice daily (once daily on weekends), pH, pCO_2, standard bicarbonate, buffer base and base excess were measured in ear capillary blood (Astrup microtechnic), together with oxygen saturation, hemoglobin, blood lactic acid and respiratory minute volume (RMV) (Wright Anemometer). Urine samples collected every two hours were examined for volume, pH, titratable acid (later total acid), sodium, potassium and creatinine. The anticipated frequency of severe respiratory acidosis did not materialize. Instead, initial pH values were relatively normal, despite RMV of 5-8 liters. Subsequently day by day there was a distinct trend toward elevation of pH to high normal and mildly alkalotic values (7.45-7.50) as recovery progressed. The mechanism for the alkaline trend has not as yet been elucidated. No consistent correlation was observed between variations in acid-base balance and in RMV or the other parameters examined. (Aided by a Fulbright grant and a John Simon Guggenheim Memorial Fellowship).

INFLUENCE OF SALINE INFUSIONS ON THE COURSE OF BARBITURATE INTOXICATION. Joseph F. Borzelleca.* Med. Coll. of Va., Richmond, Va.

Since the demonstration from this laboratory that barbiturates are absorbed from the urinary bladder, studies have been conducted to determine the influence of the urinary tract in barbiturate intoxication. The femoral veins of adult mongrel dogs were cannulated with polyethylene catheters. Barbiturate solutions and 0.9% NaCl were infused through these catheters at specific rates by means of infusion pumps. The respiratory arrest dose (RAD) and the cardiac arrest dose (CAD) were determined. With pentobarbital sodium, 1 mg/kg/ml/min, the RAD was 49 and the CAD 51 mg/kg. Administration of artificial respiration increased the CAD to 136 mg/kg. The CAD was further increased by the concomitant infusion of saline. The infusion of barbital sodium, 5 mg/kg/ml/min, resulted in a RAD of 675 and a CAD of 700 mg/kg. Artificial respiration increased the CAD to 1359 mg/kg; and again the infusion of saline elevated the CAD. The data confirm the finding that artificial respiration is beneficial in overcoming barbiturate depression and they further indicate that saline infusion in conjunction with respiratory support is more effective.
(Supported by a research grant from U. S. Public Health Service, NIH RG-7064)

THURSDAY MORNING

AUTONOMIC PHARMACOLOGY II
Lower Strong Auditorium

THE PHARMACOLOGIC SIGNIFICANCE OF CERTAIN MODEL INFLAMMATIONS. Paul M. Lish and Gordon R. McKinney. Mead Johnson Research Center, Evansville 21, Indiana.

Several types of inflammatory and anaphylactic models have been investigated with respect to their abilities to contribute to our knowledge of the inflammatory and/or allergic process, mechanisms of actions of drugs thereon, and significance of both of these parameters to the clinical management of certain disease states. Models of increased capillary permeability have been (a) rat foot edema and (b) bradykinin-induced bluing in rabbit skin. Other inflammations were ultraviolet erythema and ankle joint edema (induced by intra-articular injection of rabbit-anti-guinea-pig-serum) in guinea pigs. Classic antihistamine drugs were effective antagonists of only anaphylactoid edema; high, non-specific levels of bradykinin; and early phase of anaphylactic joint edema. The ability of certain phenothiazines (e.g. chlorpromazine and methdilazine) to act in systems affected only by such anti-inflammatory agents as aspirin and phenylbutazone, and not by classic antihistamine or -serotonin agents, offers a synthesis that tends to bridge the gap among conflicting postulates as to role of chemical mediators in local tissue injury. Demonstration of an antibradykinin property in the anti-inflammatory/ -allergic profile of a drug offers attractive speculation as to its mechanism of action.

VASODEPRESSION INDUCED BY SEROTONIN AND TRYPTAMINE THROUGH RELEASE OF ENDOGENOUS HISTAMINE. R.D.Bunag* and E.J.Walaszek Dept.of Pharmacology, Kansas Univ. Med. School,Kansas City, Ks.

Evidence has previously been presented suggesting that the depressor response to serotonin and tryptamine in the anesthetized chicken is mainly histamine mediated (Bunag & Walaszek, Fed. Proc. 20: 111, 1961). To obtain more definite proof for this mechanism, repeated injections of 48-80 were given to deplete the histamine stores of the chicken. Prior to depletion, control responses to serotonin, tryptamine, histamine and 48-80 were all depressor. Tachyphylaxis was observed following repeated administration of 48-80 and 2-3 hours after the first 48-80 injection, serotonin & tryptamine were pressor, 48-80 had no significant effect, while histamine itself was still depressor. In some animals, the ureters were cannulated and 10-minute samples of urine were collected before & after drug injections. Bioassay on the guinea pig ileum revealed the presence of significant amounts of a histamine-like substance in urine following injection of serotonin, tryptamine, histamine or 48-80 while control samples were negative. Contractions induced by the urine samples taken after drug injection could be blocked by tripelennamine. The data support the hypothesis that the depressor response to serotonin & tryptamine in the anesthetized chicken is mainly due to a release of endogenous histamine.

ENDOTOXIN, TRANSGLUTAMINASE AND PROTEIN BOUND HISTAMINE. I. Wajda*, M. Ginsburg* and H. Waelsch. Psychiatric Institute and Columbia University, New York.

The exchange of γ-amide groups of glutamine residues in protein with some primary amines is catalyzed by the Ca^{++} dependent enzyme, transglutaminase. In mice, 16 hours after a single injection of purified lipoprotein from S. typhosa the transglutaminase level in liver was increased three-fold. H. Pertussis vaccine acted similarly but is less effective in raising the enzyme level. Histamine (0.34 mmole/kg) was administered intraperitoneally to normal and endotoxin-treated mice 30 minutes before sacrifice. Liver protein was precipitated with trichloroacetic acid and traces of adsorbed histamine removed. Histamine was extracted from the hydrolysates of the liver proteins and assayed on the superfused guinea pig ileum. Hydrolysates of liver protein from normal mice with, and normal or endotoxin-treated mice without histamine injection, contained less histamine than could be detected. The liver proteins of endotoxin-treated animals after histamine injection contained significant amounts of histamine. The increase in transglutaminase level correlated with the increase in the concentration of protein bound histamine.

HUMAN BIOASSAY OF ANTIHISTAMINIC AGENTS. Peter E. Siegler*, Tibor Bodi*, Marvin A. Gershenfeld*, Elizabeth B. Brown*, and John H. Nodine*. Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Penna.

The difficulties in the clinical evaluation of antihistamines, particularly subjective factors in response, were approached by a human bioassay method. The method based on clinical observations of experienced internists and allergists uses a dose response curve like that usually applied by pharmacologists. Groups of 30 to 60 allergic patients were used to establish the dose of the antihistamine which gives significant relief to 50% of the patients. This amount of drug is one antihistaminic unit and equals the ED_{50}. Similarly the amount of drug which causes toxic effects or significant side effects in 25% of the patients (TD_{25}) was estimated. Five antihistaminic agents and placebo were used to develop the technique. These agents were N-benzhydryl-N-cinnamyl-piperazine, N-phenyl-N-benzyl-4-amino-1-methylpiperidine, cyproheptadine, dimethpyrindine maleate and tripelennamine. The ED_{50} values were 12, <100, 7, 3, and 50 mg. per day, respectively.

AUTONOMIC PHARMACOLOGY II

EFFECTS OF ADRENERGIC AGENTS ON GASTRIC SECRETION IN DOGS. Hubert W. Wingate* and S. N. Pradhan. Dept. of Pharmacology, Howard Univ. College of Med., Washington, D. C.

Gastric juice was collected from small fundal pouches (Necheles) through implanted cannula in six dogs for successive 15-minute periods. A stimulus, such as a measured quantity of food or a subcutaneous dose of histamine was given after a control period and the effects measured until the secretion returned to the original level. Three adrenergic agents - epinephrine, levarterenol and isoproterenol - selected on the basis of their divergent effects on blood vessels were injected subcutaneously. All these agents inhibited, to a varying degree, the enhanced secretion induced by the stimuli. It appears that vasoconstriction is not solely responsible for inhibition of gastric secretion by adrenergic agents, as suggested by others in case of epinephrine and levarterenol. Effects of two different types of adrenergic blocking agents exemplified by dibenzyline and dichloroisoproterenol (DCI) on such inhibition of gastric secretion are being investigated and will be discussed. (Supported by the Training Grant, HST 5384, from the National Heart Institute.)

POTENTIATION OF EPINEPHRINE BY HISTAMINE ON THE ISOLATED ELECTRICALLY STIMULATED DOG URETER. Harold H. Borgstedt.* Dept. of Pharmacology, Univ. of Rochester School of Medicine and Dentistry, Rochester, N. Y.

Isolated dog ureters were perfused at a constant rate and pressure and intermittently stimulated with alternating current. Both histamine (4 to 6 x 10^{-6} M) and epinephrine (2 to 4 x 10^{-6} M) have a stimulatory effect in this system. If, however, epinephrine was added to the bath fluid after pretreatment of the ureter with histamine in the above range of concentrations, much smaller concentrations of epinephrine (2 to 6 x 10^{-7} M) showed a stimulatory effect. The possibility is considered that histamine may sensitize certain adrenergic receptors in this organ. (Supported by U.S.P.H.S. grant B1149.)

CARDIOVASCULAR PHARMACOLOGY II
Todd West

PILOCARPINE ANTAGONISM OF THE VASODEPRESSOR RESPONSE TO ACETYLCHOLINE IN THE DOG. Joseph M. Benforado. Univ. of Buffalo School of Medicine, Buffalo, N.Y.

In dogs anesthetized with 35 mg/kg of pentobarbital, vasodepressor responses (measured with a mercury manometer) could be obtained with pilocarpine over a 1000 fold dose range. At doses of 1-10 mg the blood pressure response was biphasic with a vasopressor effect following directly on the vasodepression. When the vasodepressor response to acetylcholine was tested before and during the recovery from the effects of pilocarpine, it was evident that an antagonism was present during pilocarpine action. The dose of pilocarpine required for this effect was higher than the threshold dose for vasodepression. With large doses of pilocarpine the effect could be detected for periods up to 2 hours during which time the blood pressure had in some cases already returned to control levels. In experiments in which both acetylcholine and histamine were employed, the antagonism was found to be specific for acetylcholine. These experiments suggest that pilocarpine is a parasympathomimetic drug with dual actions. It may be considered a partial agonist with an affinity less than that of acetylcholine and with an intrinsic activity which is also probably low.

RELATIVE PRESSOR ACTIVITY OF SUBSTITUTED ACID ESTERS OF CHOLINE. A. A. Sekul* and W. C. Holland. Univ. Mississippi School of Medicine, Jackson, Miss.

Pressor activity of substituted saturated and α,β unsaturated acid esters of choline have been studied. The activity of acetylcholine has been set equal to 1. The relative pressor activity of butyryl-, β-methyl butyryl-, β-Cl-butyryl-, and α-ethyl butyrylcholine were as follows: 13, 5, 11 and 10. The values obtained for valeryl-, α-methyl valeryl-, β-methyl valeryl- and γ-methyl valeryl choline were 5, 4, 7 and 6. In the α,β unsaturated acid esters series the values for crotonyl-, α-methyl crotonyl-, β-methyl crotonyl-, α-ethyl crotonyl- and β-Cl-crotonyl choline were as follows: 7, 62, 28, 186 and 54. The acids employed in the latter series were of the trans configuration. The results will be interpreted in terms of molecular configuration and electronic activation in the carbonyl group. Particular emphasis will be placed on the importance of the magnitude of the formal negative charge on the carbonyl oxygen in determining the pressor activity of choline esters.

ACTION OF LOBELINE ON PULMONARY ARTERY PRESSURE RECEPTORS. John A. Bevan*. Dept. of Pharmacology, UCLA Medical Center, Los Angeles 24, California.

Lobeline acts on afferent endings in the pulmonary vascular bed of cats and dogs causing reflex hypotension, bradycardia and apnea. These actions are abolished by bilateral cervical vagotomy. Experiments were designed to determine the type of sensory endings stimulated by lobeline. Cats were anesthetized with α-chloralose and systemic arterial pressure and EKG were recorded. Through a right thoracotomy incision, the afferent activity of pulmonary artery pressure receptors was recorded from the peripheral end of the cardiovagal branch of the right vagal trunk described by Bianconi and Green (Arch. ital. Biol. 97: 305, 1959). Within 1-2 seconds of its injection into the right atrium, lobeline (30 µg/kg) caused an increase in rhythmic afferent activity originating from these receptors. Stimulation of the central end of this branch caused reflex hypotension and bradycardia. As the animals were artificially respired the effect of this stimulation on respiration could not be observed.

EFFECTS OF STIMULATION OF THE SPLENIC NERVES ON GAS EXCHANGE, HEART RATE AND BLOOD PRESSURE OF DOGS ON A TREADMILL. Johannes Schmier.* Dept. of Pharmacology, Harvard Med. School, Boston, Mass.

According to earlier observations the contractility of a previously depressed heart is improved by stimulation of the splenic nerves; its O_2 uptake falls. Experiments were carried out to determine whether the gas exchange of intact dogs is influenced in the same way under exercise. Five female dogs, fitted with gas mask and with a catheter in the aorta, were exercised on a treadmill (5 mph). Expiration volume, O_2 uptake, CO_2 output, blood pressure and heart rate were electrically determined and recorded. In every second experiment the splenic nerves were stimulated for 20 sec during the 7th min after beginning of exercise (16 observations). Compared to the 14 control observations, the O_2 uptake and CO_2 output fell after stimulation, as did the heart rate. The fall in O_2 uptake averaged 46.6 ml/min. The blood pressure remained unchanged. Signs of exhaustion, which were manifest at the 7th min of exercise, were improved after nerve stimulation. The dogs were exercised until they ceased to run. After nerve stimulation, the running time rose from 13.1 to 16.3 min (mean values). After exercise was completed, the return of the gas exchange to normal was identical in both series of experiments.

THURSDAY MORNING

CARDIOVASCULAR PHARMACOLOGY II

CARDIOVASCULAR EFFECTS OF RESERPINE IN THE RENOPRIVAL HYPERTENSIVE DOG. R.L. Bowe* and R.R. Overman*, Univ. of Tenn. School of Med., Memphis, and Med. Col. of S. C., Charleston.

While Reserpine is known to reduce blood pressure in experimental renal hypertension, its effects upon renoprival hypertension had not been investigated. To determine the cardiovascular effects of Reserpine upon renoprival hypertension, 10 bilaterally nephrectomized dogs, maintained 22 days by peritoneal dialysis, were administered 0.01 mg/kg/day Reserpine on days 1 to 6 and 11 to 14. During days of reserpinization, blood pressure was held 12% below control levels; during days 7 to 10 and 15 to 22 when Reserpine was withheld, blood pressure rose to 72% above control levels. Also attributable to Reserpine action was a significant decrease in peripheral resistance, circulation time, and time lapse between initial fluorescein appearance and peak fluorescence. There was some increase in stroke volume and a variable effect upon the cardiac output. Attributable to the renoprival state itself was an overall decreased hematocrit hemoglobin level, blood volume, cardiac output, and increased peripheral resistance, circulation time and time lapse during those periods when Reserpine was withheld. Reserpine was shown to reduce blood pressure in renoprival hypertension and to produce cardiovascular effects similar to those seen in other hypertensions.

A NON-DIURETIC BENZOTHIADIAZINE WITH ANTIHYPERTENSIVE PROPERTIES. A. A. Rubin,* S. C. Beauregard,* L. M. Hausler,* L. Zitowitz* and M. M. Winbury. Dept. of Pharmacology Schering Corp., Bloomfield, N. J.

On the basis of previous in vitro studies, we have assumed that the antihypertensive action of benzothiadiazine diuretics may be due to a direct vascular action independent of any renal effects. In exploring this possibility, certain des-sulfamyl benzothiadiazines were selected (e.g., 3-methyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide, SRG 95213) which are non-diuretic and yet directly affect vascular smooth muscle. In isolated aortic strip preparations, both SRG 95213 (10^{-6}, w/v) and benzothiadiazine diuretics (10^{-4}, w/v) nonspecifically antagonized the submaximal contractions induced by various vasoactive agents. In chronic studies on hypertensive rats and dogs, SRG 95213 produced a gradual and sustained antihypertensive effect. In acute studies on anesthetized dogs, single i.v. injections of SRG 95213 reduced arterial pressure but reflexly increased cardiac output and myocardial contractile force without decreasing right atrial pressure. Intra-arterial injections into various canine vascular beds increased the rate of blood flow. Data from these and other studies indicate that SRG 95213 lowers blood pressure by inducing direct peripheral vascular relaxation. Its site of action may be primarily arteriolar.

PHARMACOLOGY OF 3-METHYL-7-CHLORO-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDE (SRG 95213), A NON-DIURETIC ANTIHYPERTENSIVE AGENT. F. E. Roth, S. Tozzi,* T. Eytel* and V. Begley.* Dept. of Pharmacology, Schering Corp., Bloomfield, N. J.

Unlike chlorthiazide or other sulfamyl-containing benzothiadiazines, SRG 95213 produced an immediate and prolonged hypotensive response when administered i.v. to anesthetized dogs or cats. At 10 mg/kg the mean blood pressure of dogs was reduced 40-60 mm Hg, pulse pressure increased and a prolonged bradycardia was observed. The pressor responses to bilateral carotid occlusion or injections of l-epinephrine or l-norepinephrine were partially blocked. SRG 95213 produced a hypotensive response following pretreatment with chlorisondamine, phentolamine, hydralazine, atropine, chlorpheniramine, reserpine or dichloroisoproterenol. Spinal cord transection or bilateral vagotomy with carotid sinus extirpation in cats did not prevent the hypotensive action of SRG 95213. Hypotensive doses of this des-sulfamyl benzothiadiazine in cats (2-10 mg/kg) did not alter the nictitating membrane response to stimulation of the pre- or post ganglionic cervical sympathetic nerve. The membrane response to i.v. epinephrine also was unaffected, which is in marked contrast to the action of adrenergic blocking agents. These and other data reported at this meeting indicate that the primary action of SRG 95213 is a direct and prolonged peripheral vasodilation.

ANALGESICS
Lattimore 109

THE DEVELOPMENT OF TOLERANCE TO THE ANTIDIURETIC EFFECT OF LEVORPHANOL IN RATS. James M. Fujimoto, Heber H. Newsome* and Wayne Tobin*. Tulane Univ. School of Med., New Orleans, La.

It was reported earlier that chronic administration of levorphanol to rats led to the development of polydipsia and polyuria. The present studies were aimed toward following the time course of development of these effects. Male Sprague Dawley rats (40 or more to each of 3 groups) were injected twice daily (8 a.m. and 8 p.m.) with levorphanol tartrate. The response of these rats to a standard water load (5% body weight, p.o.) was tested by measuring the water excretion time (Burn et al.). During the earlier phases of levorphanol administration, excretion times were prolonged thus indicating the expected antidiuretic response. As chronic treatment was continued, tolerance developed to this effect of levorphanol in that the excretion times returned toward normal. In the 2 groups where the dose of levorphanol was rapidly increased so that doses of 60 mg/kg were being given by day 7 or 14, the excretion times not only returned toward normal but were significantly shorter than normal. These latter rats, if given free access to water, exhibited polydipsia and polyuria. (Supported by a grant from USPHS).

CERTAIN ASPECTS ON THE MECHANISM OF DEVELOPMENT OF TOLERANCE TO THE ANTIDIURETIC EFFECT OF LEVORPHANOL IN RATS. Heber H. Newsome*, Wayne Tobin* and James Fujimoto. Tulane Univ.School of Med., New Orleans, La.

Concurrent studies were carried out on Sprague-Dawley rats (40 or more to each of 3 groups) which were being chronically treated with 2 daily doses of levorphanol and were developing tolerance to the antidiuretic effect of levorphanol. The effects on the excretion time (of a 5% water load, Burn et al.) of the following drugs were tested: levallorphan, 10 mg/kg, pituitrin and pitressin .16 units/kg, and nicotine, 5 mg/kg, all s.c. Levallorphan antagonized the antidiuretic effect of levorphanol and in addition, a diuretic response was obtained. This dose of levallorphan by itself had no effect on excretion time in normal rats. During the late stage of levorphanol treatment when the rats had developed an increased ability to handle the water-load, levallorphan again reversed the levorphanol effects so that now an antidiuretic response was obtained to the levallorphan. For considering the response of the levorphanol treated rats to ADH, responses to pituitrin and pitressin were found to become gradually observable as tolerance developed to the antidiuretic effect of levorphanol. With the nicotine test, there seemed to be some impairment of the endogenous ADH mechanism in these rats. (Supported by a grant from USPHS.)

THE INFLUENCE OF N-ALLYL OXIMORPHONE ON THE RESPIRATORY EFFECTS OF OXYMORPHONE IN ANESTHETIZED MAN. J. N. Lunn*, F. F. Foldes, J. Moore* and I. M. Brown* Dept. of Anes, Marcy Hospital and Univ. of Pgh. School of Medicine, Pittsburgh, Pa.

Ten patients (Group I) were premedicated with 100 mg pentobarbital sodium and 0.4 mg scopolamine. Ten others (Group II) also received 100 mg meperidine. Both groups were lightly anesthetized with thiopental and N_2O-O_2. Subsequently, members of Group I received at 0 time, 5 γ/kg N-allyl oxymorphone and at 5 minutes 20 γ/kg oxymorphone. In Group II, 20 γ/kg oxymorphone was administered at 0 time and 5 γ/kg N-allyl oxymorphone at 7 minutes. All drugs were injected intravenously. Respiratory and circulatory measurements were made at 0, 3, 8, 11 and 15 minutes in Group I, and at 3, 6 and 10 minutes in Group II. In Group I, after N-allyl oxymorphone, no significant respiratory or circulatory changes developed. The subsequent injection of oxymorphone produced a 23 and 18% decrease of the respiratory rate and minute volume, respectively. In Group II, the administration of oxymorphone produced apnea in 3 out of 10, and bradycardia in all subjects, and a mean decrease of 68, 25 and 65% of the respiratory rate, tidal and minute volumes, respectively. The administration of N-allyl oxymorphone at 7 minutes antagonized the respiratory depression so that at 10 minutes, the respiratory rate, tidal and minute volumes were 94, 146 and 140% of control, respectively.

EFFECT OF WITHDRAWAL AND NALORPHINE ON CEREBRAL CORTICAL SLICES ADAPTED TO MORPHINE. A. E. Takemori. State Univ. of N. Y., Upstate Medical Center, Syracuse, N. Y.

Recently, using standard manometric technics for measuring oxygen uptake, this laboratory demonstrated that cellular adaptation to the depressive effect of morphine occurred in cortical slices of brain obtained from chronically morphinized rats. In studying the rate of development of this adaptation, rats were injected IP 15 mg/kg morphine SO_4 b.i.d. for varying number of days. Complete cellular adaptation of the cortical slices from such rats occurred within a week. Upon abrupt withdrawal, the adaptation was lost after 7 days of abstinence, and the slices again became sensitive to the depressive effect of morphine. When 10 mg/kg nalorphine was injected IP to rats previously morphinized for 7-10 days 30 min prior to sacrifice, the cortical slices from such animals became sensitive to morphine showing an acute reversal of cellular adaptation. Various conc. of nalorphine were used in combination with morphine to study the reversal effect in vitro. The optimum reversal was seen when the antagonist:agonist ratio was 1:4 and 1:10. (Supported by National Institute of Mental Health grant No. M-3897, USPH)

THE ANTITUSSIVE ACTIVITY OF A SERIES OF DIALKYL-AMINODIPHENYLBUTANOL ESTERS. Joseph A. Miller, Jr.,* Donald B. Meyers* and E. Brown Robbins.* Eli Lilly and Company and Butler Univ. College of Pharmacy, Indianapolis, Indiana.

The effect of structural modifications upon the antitussive activity of a series of dialkylaminodiphenylbutanol esters was examined. In an attempt to investigate a possible correlation of pharmacological activities, the compounds were also evaluated for their spasmogenic effect upon the intestine and their analgesic activity. Antitussive activity was determined in guinea pigs by means of SO_2-induced cough. Spasmogenic activity was determined by inserting a balloon into the duodenum of anesthetized dogs. Analgesic activity was determined by the rat-tail heat method. The optimum antitussive structure tested within this series was α-dl-2-propionoxy-1,2-diphenyl-3-methyl-4-dimethylaminobutane HCl. The optimum analgesic structure tested in this series was the 2-acetoxy analogue of the same compound. Some degree of correlation was shown among the activities, although exceptions were noted.

PRECLINICAL EVALUATION OF PRODILIDINE HYDROCHLORIDE FOR PHYSICAL DEPENDENCE AND TOLERANCE. J. R. Albert,* A. G. Wheeler,* H. C. Hawkins* and J. W. Kissel.* Mead Johnson Research Center, Evansville, Indiana.

Prodilidine HCl (1,2-dimethyl-3-phenyl-3-pyrrolidyl propionate HCl) was reported previously (Fed. Proc. 20: 309, 1961) to be a non-narcotic analgesic with the potency of codeine. In preparation for a clinical evaluation of physical dependence and tolerance, both rats and dogs were dosed t.i.d. with increasing amounts of prodilidine HCl. Maximum tolerated doses were achieved by 4 wks. and maintained for an additional 2 wks. Morphine sulfate was administered on an appropriately similar schedule. Drugs were withdrawn and observations made to determine whether natural or nalorphine-induced abstinence signs would appear and to observe the effects of cross-over dosing. At 6 wks. the maximum tolerated doses t.i.d. of prodilidine HCl were 200 mg./kg., s.c. in the rat, and 14 mg./kg. i.v. in the dog. No withdrawal signs were noted in dogs and only questionable signs were evident in rats withdrawn from prodilidine. Dose levels of 75 mg./kg. s.c. in the rat, and 10 mg./kg. i.v. in the dog of morphine caused physical dependence and tolerance. In cross-over experiments, some tolerance was observed in prodilidine treated rats and especially in dogs to the CNS depressant effects of morphine. In contrast, there was no cross-tolerance in morphine-dependent rats or dogs to the toxic side effects of prodilidine.

PHARMACOLOGICAL STUDIES OF PIPAZETHATE (THERATUSS)-A NEW ANTITUSSIVE. R. Laffan.* The Squibb Institute for Medical Research, New Brunswick, N. J.

Pipazethate (10H-pyrido[3,2-b][1,4-benzothiazine-10-carboxylic acid, ester with 2-(2-piperidinoethoxy)ethanol, hydrochloride) has been reported to be an effective antitussive in animals and to exhibit in man the same potency as codeine, with no undesirable side effects. In dogs, we found it had approximately 60% the potency of codeine in reducing cough due to electrical stimulation of the tracheal submucosa. Definite reduction in intensity and frequency of induced cough occurred at 1/40th the LD_{50} in this species. The drug displayed no tranquilizing activity and no sedative activity in mice and rats. Convulsions preceded death in rodents, cats, and dogs but the animals exhibited little or no excitement at sub-convulsive doses. There was no effect upon blood pressure, resting or stressed, at sub-lethal doses. No antagonism of the action of histamine, serotonin or acetylcholine was seen either in vivo or in vitro. High doses produced myocardial arrhythmias in vivo and negative inotropic and chronotropic effects in the perfused cat heart. The oral LD_{50}'s of pipazethate ranged widely from 80 mg/kg in dogs through 207 in mice to 530 in rats. The i.v. LD_{50}'s in the three species varied less (8 to 17 mg/kg).

THE EFFECT OF A PHOSPHATIDO-PEPTIDE FRACTION OF INTESTINE ON THE INTESTINAL ABSORPTION OF A QUATERNARY AMMONIUM DRUG. Ruth R. Levine. Dept. of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, Mass.

Previous studies showed that intestinal mucus and polysaccharides extracted from mucus inhibited the absorption of onium compounds. In contrast, in the present studies, an extract of the entire rat ileum was found to increase markedly the in vivo absorption of the quaternary drug, benzomethamine (N-diethylaminoethyl-N'-methylbenzilamide methobromide). This extract was the phosphatido-peptide fraction (Huggins and Cohn: J. Biol. Chem. 234:257, 1959). When the phosphatido-peptide was added with benzomethamine to in vivo intestinal loops of rats, the 3 hour absorption of benzomethamine was significantly increased from mean control levels of 20% up to 60%. The degree of increase in absorption was a function of the amount of phosphatido-peptide in the intestinal loop. Preliminary in vitro evidence has been obtained for the formation of a complex of the phosphatido-peptide and benzomethamine. This is the first evidence that intestinal absorption of an onium compound can be enhanced by material extracted from tissue. (Supported in part by Grant B-1966 from the Institute of Neurological Diseases and Blindness of the National Institutes of Health.)

THE EFFECT OF INSULIN ON THE FLUX OF POTASSIUM IN ISOLATED FROG MUSCLE. D. R. H. Gourley. Dept. of Pharmacology, Univ. of Virginia School of Medicine, Charlottesville.

Isolated intact sartorius muscles of the frog were placed in K-free Ringer's solution at 5°C for 18 hours to reduce their K content to about 70% of normal. Immediately after transfer to Ringer's solution containing 10 mEq K/l (20°C), K influx > K efflux. During this phase of the recovery period, muscles exposed to insulin (0.05 U/ml) take up less K than the corresponding control muscles but later the insulin-treated muscles appear to take up more K than the controls. K efflux was studied in a separate experiment by loading muscles with K^{42} in a preliminary incubation and measuring the K^{42} released into non-radioactive Ringer's solution. Under these conditions insulin slowed K efflux from 8.1 % hr^{-1} to 7.1 % hr^{-1} which accounted for most of the net increase in muscle K observed concomitantly. The increase in muscle K caused by insulin is therefore probably the net result of inhibition of K efflux combined with a less significant inhibition of K influx by the hormone.

CALCIUM ANTAGONISTS ON SMOOTH MUSCLE FUNCTION. Leon Hurwitz, Frank Battle* and George Weiss*. Dept. of Pharmacology, Vanderbilt Medical School, Nashville, Tenn.

The sustained contraction of an isolated K-depolarized ileal smooth muscle from guinea pig can be inhibited by cocaine or ethanol. Adding excess calcium ion to the bathing medium will antagonize the inhibition. When high concentrations of inhibitory drug (7% ethanol or 1.8 x 10^{-3}M. cocaine) and calcium ion are used, the stimulatory effect of calcium ion can be potentiated by acetylcholine. A 10 fold variation in the concentrations of cocaine and calcium ion does not alter appreciably the level of response of the tissue providing the ratio of the two agents is kept constant. This is not true for the ethanol-calcium antagonism. These data suggest that the antagonism between cocaine and calcium ion on depolarized smooth muscle tone is competitive, whereas the antagonism between ethanol and calcium ion is not.

We have observed that the increase in K efflux which acetylcholine elicits in an ileal muscle is inhibited much more effectively by ethanol in a bathing medium containing one-fifth calcium ion than in normal Tyrode's solution. Possibly, in this instance, the inhibition of potassium movement is also linked to the antagonism between ethanol and calcium ion.

ROLE OF COPPER IN THYROXINE POTENTIATION OF IN VITRO EPINEPHRINE ACTION ON SMOOTH MUSCLE. S. B. Barker and Hiroshi Shida*. University of Alabama Medical Center, Birmingham, Alabama.

Thyroxine (T_4) and many of its analogs increase the tension and delay relaxation of epinephrine- and norepinephrine-induced contractions of blood vessel smooth muscle when ordinary reagent grade chemicals and distilled water are used for solutions. In confirmation of Shemano and Fallon (Proc. Soc. Exper. Biol. Med., 103, 282, 1960) implicating copper contamination in this reaction, we have found no T_4 enhancement when selected reagents and glass-redistilled water result in a copper content of 1.5 µg/l for the bath fluid. Addition of 5 µg. of copper per l. depresses the response to epinephrine and permits T_4 or ethylenediaminetetraacetate potentiation. Zn and Mn are also effective, but only the Zn is reversed by T_4. (Supported by grants from the U.S.P.H.S. (A-1545) and the Alabama Heart Association.)

POTASSIUM-42 ACCUMULATION IN THE EXCISED CORNEA OF THE DOG. Merle W. Riley*. Dept. of Pharmacology, Coll. of Med., Univ. of Cincinnati, Cincinnati, Ohio.

Freshly excised corneas were placed in chambers so that the epithelial and endothelial surfaces were each in contact with the separate bathing solutions which replaced the tear and aqueous fluids. One solution at a time contained K^{42}. The corneas were exposed for four hours at room temperature. In the presence of intact epithelium and endothelium the accumulation of K^{42} per gram of cornea was 16 times larger when the radioactive solution was placed on the endothelial side than when placed on the epithelial side. Removal of the epithelium extinguished this ratio: the cornea accumulated the same amount of K^{42} from either side, reflecting a decrease in the accumulation from the endothelial side and an increase from the epithelial side as compared with intact corneas. Removal of the endothelium did not alter the 16:1 ratio, but reduced the values for accumulation from either side by one-half. Removal of both the epithelium and endothelium reduced the ratio to 2:1. When ouabain (10^{-6}M) was added to the bathing solution containing K^{42} with both epithelium and endothelium intact the ratio was reduced to 6:1. The K^{42} accumulation was decreased when the ouabain and K^{42} were placed on the endothelial side and increased when placed on the epithelial side.

Na, K, Ca, and Cl EXCHANGE IN GUINEA PIG ILEUM. N. Chujyo* and W. C. Holland. Univ. of Miss. Sch. of Medicine, Jackson, Mississippi.

Fluxes of Na, K, Ca and Cl in tubular segment (mucosa inside) of guinea pig ileum were studied. Na: The initial absolute influx and efflux were estimated to be 11 and 24 pmole $cm^{-2}sec^{-1}$, respectively; both of which varied with time. The fluxes, as well as time course of Na content in the tissue, suggest the existence of active outflow of Na which diminished with time. Pilocarpine (5 x 10^{-6}M) had little or no effect on Na exchange during an initial 30 min interval. K: Influx and efflux were estimated to be 1.7 and 3.8 pmole $cm^{-2}sec^{-1}$, respectively. Pilocarpine caused a temporary increase in efflux and a slight decrease in influx. Ca: Time course of Ca inflow and outflow were complex suggesting a heterogeneous type of exchange. Pilocarpine increased the rate of Ca exchange presumably by releasing Ca from a bound form in the tissue. This effect is believed to be the molecular basis of pilocarpine induced contraction. Cl: Initial influx and efflux were estimated to be 3.5 and 5 pmole $cm^{-2}sec^{-1}$, respectively. Fluxes changed with time and were temporarily depressed by pilocarpine.

WHOLE-BODY CARBOHYDRATE METABOLISM IN THE IRRADIATED RAT. J. L. Spratt* and G. V. LeRoy*. Argonne Cancer Research Hospital†, and Depts. of Pharmacol. and Med., U. of C., Chicago, Ill.

Although metabolic alterations in DNA metabolism, carbohydrate metabolism, etc., have been noted in the irradiated animal, there is no adequate explanation of the metabolic alterations leading to death. We studied this problem in the intact animal exposed to whole-body x-irradiation by observation of in vivo metabolic transformations as reflected in the oxidation of C^{14}-labeled intermediates to respiratory $C^{14}O_2$. Female Sprague-Dawley rats 70-90 g were studied at various times (0-48 hr) after various doses of radiation (0-800 r). Food, but not water, was withheld during the experiment. Animals were injected I.P. or I.V. with labeled bicarbonate, formate, acetate, fructose, glucose, or ribose. The animal was then placed in a continuously recording respiratory $C^{14}O_2$ monitoring system for 1-3 hr. Preliminary results indicate that x-irradiation does not markedly influence metabolism of bicarbonate, formate, and acetate, although starvation has some effects. Studies on fructose-U-C^{14} metabolism at 48 hr after irradiation indicate that the marked difference noted following I.P. administration is due to absorption, since no difference was noted upon I.V. administration. (†Operated by the University of Chicago for the United States Atomic Energy Commission.)

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SOME FACTORS MODIFYING THE EFFECTS OF ESERINE ON CORTICAL EVOKED POTENTIALS. W. D. Winters, J. Siegel* and A. J. Hance*. Dept. of Anat., U. of Cal. Med. Ctr., Los Angeles, California.

Previous studies (The Pharmacologist, 2: 78, 1960) have shown that in flaxedil immobilised cats 0.1 mg/kg eserine sulphate (ES) i.v. has little effect on superficial cortical evoked responses (SCR) at motor, somatic sensory and visual cortices if premedication with atropine methylnitrate (AMN) has been used to block peripheral autonomic effects. However, the SCR at the median suprasylvian gyrus (MSS) is greatly reduced. Present investigations show the following: 1) Pentobarbital anesthesia blocks the effect of ES on MSS in unpremedicated cats; 2) stimulation of the reticular formation (RF) reduces the SCR most at MSS and least at visual cortex. ES produces a fall in amplitude at MSS but not at motor cortex, while subsequent RF stimulation fails to lower MSS further but still lowers SCR in motor areas; 3) in neuronally isolated islands of MSS the SCR is unaffected by RF stimulation or by ES while in adjacent intact MSS the SCR is markedly reduced by either. The results are in agreement with our hypothesis that ES does not have a direct action on superficial cortex. The differential action of RF stimulation and ES on motor cortex implies that different mechanisms for the attenuation of SCR are involved. The protection of the SCR by pentobarbital in animals unpremedicated with AMN suggests that in these part of the action of ES may be secondary to peripheral autonomic changes.

SYNAPTIC INHIBITION BY SEROTONIN IN ISOLATED CEREBRAL CORTEX. Jose M. Rodriguez*, E. Ross Hart and Amedeo S. Marrazzi. Vet. Admin. Research Labs. in Neuropsychiatry. Pittsburgh 6, Pa.

In our previous descriptions of cerebral synaptic inhibition by close arterial (intracarotid) injections of minimal doses of serotonin, LSD-25 and related substances, we have ascribed the action principally to the terminal synapses from which we were recording the transcallosally and the cortico-cortically evoked potentials. The preservation of an unaltered inhibition by serotonin, etc., after various degrees of undercutting and sectioning resulting in:- a) a cortical slab of suprasylvian and lateral gyri, b) a transcallosal preparation isolated from brain stem, c) a transcallosal preparation isolated from brain stem and basal ganglia, have convinced us that the cerebral synaptic inhibition described can be obtained independently of effects on subcortical or remote cortical neurons. The latter are however susceptible to suitable doses of synaptic inhibitors delivered by suitable routes.

BRAIN CHOLINESTERASE INHIBITION AFTER DIMETHYL CARBAMATE OF DEOXY DEMETHYL LYCORAMINE, PHYSOSTIGMINE OR NEOSTIGMINE. M. M. Hein* and R. L. Irwin. National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland

The dimethyl carbamate of deoxy demethyl lycoramine hydrochloride (HCDL), the methiodide analog (MCDL), neostigmine bromide or physostigmine salicylate were injected into rats at equimolar doses corresponding to the LD_{20} of HCDL (1.01 mg/Kg) and the LD_{20} of MCDL (0.108 mg/Kg). Rats were sacrificed from 5 to a maximum of 180 min. after drug injection. The forebrains were removed, and analyzed for CHE activity by automatic potentiometric titration. Brain CHE was not inhibited by MCDL. HCDL showed maximal inhibition at 30 min. with recovery to no inhibition at about 100 min. Physostigmine produced maximal CHE inhibition during the first 20 min. after injection with a proportionately earlier recovery. With neostigmine at each dose level about one third of the animals showed a significant CHE inhibition. In vitro MCDL and HCDL are about equally potent as inhibitors of brain CHE ($I_{50} = 1 \times 10^{-8}$M).

CENTRAL AND PERIPHERAL EFFECTS OF AMITRIPTYLINE AND ETHYLTRYPTAMINE. H. Sabelli*, J. Levin*, L. Seigler*, and J. Toman. Chicago Medical School, Chicago, Illinois.

Two new clinical investigational antidepressive drugs were studied by a variety of procedures in experimental animals. The drugs were amitriptyline ("Elavil") and alpha ethyltryptamine ("Monase"). Both isomers of the latter were tested. Test methods included blood pressure of pentobarbital-anesthetized dog, EEG and EKG of unanesthetized rabbit, nerve conduction in frog sciatic, and various observations in mice including motor behavior, electroshock seizure pattern, response to vibration stress, autonomic functions, and barbiturate potentiation. A wide variety of interactions with autonomic agents were studied in an effort to delineate mechanisms of action. Amitriptyline and ethyltryptamine were similar chiefly in that they had moderate anticonvulsant effects but also caused minor seizures. Otherwise they were notably different and usually opposite but not mutually antagonistic in central nervous and cardiovascular autonomic effects. In most respects amitriptyline behaved like imipramine, and ethyltryptamine was predominantly amphetamine-like. The (-) isomer of ethyltryptamine was much weaker than the (+) isomer.

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EFFECTS OF CO_2 ON REFLEX AND CENTRAL CONTROL OF RESPIRATION IN CATS. R. Rosenstein# and H.L. Borison. Dept. of Pharmacology, University of Utah, College of Medicine, Salt Lake City.

Alterations in spontaneous respiration and in electrical reactivity of the medullary inspiratory integrator were studied in unanesthetized cerveau isolé cats. In such cats, 5% CO_2 consistently enchanced both rate and depth of ongoing respiration. In 4 of 5 cats with cranial nerves IX and X severed, CO_2 reduced the rate of breathing but respiratory minute volume was still augmented owing to an even greater increase in depth. Indeed, a forced expiratory interphase became evident after CO_2 in the debuffered cats. Central reactivity was judged by (1) stimulus threshold for respiratory baseline shift (integrator sensitivity); (2) threshold for sustained inspiration (modulator drive); (3) maximum elicitable inspiratory movement (integrator drive). A change in stimulus threshold for baseline shift was not detected after CO_2. Stimulus threshold for sustained inspiration, however, was clearly increased by CO_2 in all cats, whether buffer-nerve intact or debuffered. In both cases, maximum inspiratory response was augmented only slightly (<10%) by CO_2 at a stimulation frequency of 50 cps but was enchanced considerably (up to 50%) at 100-300 cps. The results indicate that CO_2 has little influence on integrator sensitivity but increases both modulator and integrator drive. (Supported by USPHS Grant B-491.) #NIH Predoctoral Fellow BF-7870.

CHARACTERIZATION OF RIGIDITY FOLLOWING SPINAL CORD ISCHEMIA. Satoshi Murayama* and Cedric M. Smith. Dept. of Pharmacology, Univ. of Illinois College of Medicine, Chicago 12, Illinois.

Ischemia of spinal cords of cats was produced by clamping the thoracic aorta, with or without simultaneous occlusion of the internal mammary arteries. With 20 to 40 min occlusion there were no gross changes in muscle function 24 hours postoperatively in 11 cats; occlusion of 45 to 60 min resulted in marked persistent tonic extensor rigidity of hind limbs in 12 of 38 animals, permanent flaccid paralysis in 8, no change in 14 and 4 died. In cats manifesting rigidity there were no hind-limb flexor or crossed reflexes; electrically-induced L_7 monosynaptic reflex potentials were either normal or enhanced, whereas polysynaptic potentials were markedly reduced or not detectable; forcible flexion of the foot appeared to be painful. After 5-10 days the knee and ankle joints were alkylosed and the muscles atrophied. These results are consistent with those obtained with dogs by Gelfan and Tarlov (J. Physiol. 146: 594, 1959) who postulated that this rigidity is the result of destruction of interneurons with spontaneous repetitive activity of motoneurons. The force opposing phasic and sustained flexion of the ankle was accurately measured and found to be decreased by sodium pentobarbital (5-10 mg/kg) or mephenesin (6.25-25 mg/kg). (Supported by Grant B-973 USPHS.)

EFFECT OF 2,2-DIPHENYL-4-(2-PIPERIDYL)-1,3-DIOXOLANE HCL (CL-639-C) ON THE GASTROINTESTINAL TRACT. C. R. Thompson*, B. Williams*, L. Hershberger*, and J. Hidalgo, Research Div., Cutter Labs., Berkeley, Calif.

In vitro CL-639-C was found to be a weak anti-cholinergic about 1/200th the potency of atropine, but it was equally potent as atropine in antagonizing the contraction of isolated rabbit ileum induced by DMPP. CL-639-C was more potent than papaverine in antagonizing the spasmolytic effect of BaCl2. In vivo CL-639-C decreased the distance travelled by an indicator in the GI tract of rats. In dogs the spontaneous motility of the GI tract was decreased and the spasm induced by BaCl2, 5 mg/kg i.v. relaxed but rarely prevented. In Thyry Vella loop dogs oral administration of CL-639-C decreased the spontaneous motility of the loop and topical application greatly delayed the passage of a bolus. CL-639-C decreased the gastric secretion of pylorus ligated rats and decreased the number and severity of ulcers in Shay rats. Cortisone induced ulcers in rats were prevented by CL-639-C. Other properties of the compound include local anesthesia, mild diuretic and anti-inflammatory properties.

AUTONOMIC AND CENTRAL EFFECTS OF 2,2-DIPHENYL-4-(2-PIPERIDYL)-1,3-DIOXOLANE HCL (CL-639-C). John Hidalgo, Joel Gallin*, B. Williams* and C. R. Thompson*, Research Div., Cutter Labs., Berkeley, Calif.

Administration of CL-639-C results in loss of the righting reflex with retained awareness and without muscle flacidity. The loss of the righting reflex occurs at a dose level of 3% the LD50, intravenously in rabbits and at about 12.5% of the LD50 orally in dogs. CL-639-C potentiates barbiturate induced hypnosis. The response of mice to a thermal stimulus is quickened by CL-639-C. In cats, CL-639-C blocks the blood pressure response to peripheral vagal stimulation but not to intravenous acetylcholine 0.1 microgm/kg. The response of the nictitating membrane to preganglionic stimulation remains unaffected. In dogs the response of the submaxillary gland to stimulation of the chorda tympani nerve is decreased but the salivary response to intravenous acetylcholine is increased. Postganglionic potentials of the ciliary ganglion in cats and dogs are abolished or decreased by CL-639-C. Study of cardiovascular reflexes in dogs demonstrate vagal block but no interference with the pressor response to carotid occlusion. The parasympathetic component of DMPP is decreased or abolished but the response to exogenous acetylcholine is retained or decreased depending on dosage. The mechanism of action of CL-639-C is believed due to preferential parasympathetic ganglionic block.

A NEW AND SIMPLE METHOD FOR THE QUANTITATIVE EVALUATION OF AUTONOMIC DRUGS. W.T. Beaver* and W.F. Riker. Cornell University Medical College, New York.

Enucleated mouse or rat eyes with pigmented irides were maintained in Kreb's - HCO_3 Ringer and used to test the activity of drugs affecting a parasympathetic neuroeffector. Eyes were mounted in sockets drilled in black lucite trays. These were then immersed in a lucite chamber containing the bathing solution held at 37°C. and equilibrated with 95% O_2 - 5% CO_2. Pupil diameter was measured through a microscope, fitted with an ocular micrometer disc. The preparation showed no signs of deterioration over 4 hours. Log dose-response lines were constructed from mouse eye responses for physostigmine, neostigmine, ACh and TMA; all were parallel and the respective ED 50's were: 2×10^{-5}M.; 2.5×10^{-4}M.; 10^{-3}M.; 2×10^{-3}M. ACh antagonism by atropine and potentiation by physostigmine were quantitatively demonstrated. Mouse eye was 10 times more sensitive to ACh than rat eye. Removal of the cornea in the rat increased sensitivity to ACh by ca. 4,500 times. The method has provided a remarkably precise and efficient means for quantitative drug evaluation.

CHOLINOMIMETIC EFFECTS OF HIGH DOSES OF 2-FORMYL-1-METHYLPYRIDINIUM IODIDE OXIME (2-PAM). A. M. Kunkel, J. F. O'Leary and A. H. Jones*. Pharmacology Branch, U. S. Army Chemical Research & Development Laboratories, Army Chemical Center, Md.

High doses of 2-PAM (40 mg/kg and higher) produce marked cholinomimetic effects in mice, rabbits, cats and dogs. The principal effects are lacrimation, salivation and muscular fasciculation. In vivo, gut activity is increased. The responses to injected acetylcholine of both skeletal muscle excited by indirect electrical stimulation and the nictitating membrane are increased by 2-PAM. All of these actions except the somatic neuromuscular response are antagonized by atropine. Lethal doses of 2-PAM have actions similar to those in anticholinesterase poisoning; rabbits poisoned with a lethal dose of 2-PAM can be saved by atropine given with the oxime. However, the mild bradycardia and transient depressor effect of therapeutic doses of 2-PAM are not prevented by prior atropine. The cholinomimetic action of 2-PAM on skeletal muscle has been reported previously (Wills et al., Proc. Soc. exp. Biol., N.Y., 101: 196, 1959).

PHARMACOLOGICAL PROPERTIES OF OXOTREMORINE, AN ACTIVE METABOLITE OF TREMORINE. Wilford L. Haslett* and Donald J. Jenden. Dept. Pharmacol., UCLA Medical Center, Los Angeles 24, Calif.

Tremorine, 1,4-dipyrrolidino-2-butyne, produces Parkinson-like tremors and marked parasympathomimetic effects in a variety of animals. The formation of an active metabolite of this compound in vitro was demonstrated by Kocsis & Welch (The Pharmacologist, 2: 87, 1960). This metabolite has recently been shown to be 1-(2-oxopyrrolidino)-4-pyrrolidino-butyne-2 (oxotremorine) (Cho, Haslett & Jenden, Biophys. Biochem. Res. Comm., in press), and is about 1000 times as active as tremorine in regard to both central and parasympathomimetic effects. Oxotremorine is a slightly more potent depressor agent than acetylcholine, and causes an immediate transient fall in arterial pressure in dogs and cats under chloralose or pentobarbital anesthesia. After vagotomy or ganglionic blockade this fall in arterial pressure is accompanied by pronounced bradycardia. Atropine completely abolishes both the hypotension and bradycardia, and there is no pressor response to large doses of oxotremorine after atropinization. The effects of this compound on smooth muscle in vitro are typically cholinergic, and its actions on the isolated guinea pig bladder and ileum are similar to those produced by carbachol. Oxotremorine has no effect on the neuromuscular junction (guinea pig diaphragm) at a concentration of 8.5×10^{-5} M, and does not inhibit serum or red cell cholinesterase (dog) at a concentration of 1.0×10^{-4} M.

INFRARED ANALYSIS OF CHOLINE ESTERS. Nedra Jordan* and Joseph V. Auditore.* *Departments of Pharmacology, Meharry Medical College and Vanderbilt Medical School, Nashville, Tennessee.*

Infrared has been applied with some success in distinguishing between the members of a homologous series and some of the naturally occuring choline esters. In this homologous series the relative intensity of the methylene rocking vibration at 720cm^{-1} increases progressively as the chain is lengthened. A progression of absorption bands is observed between 1180 and 1350cm^{-1} these changes are induced by alteration of the chain length. The principal absorption bands are assigned to the vibrations of specific molecular groups. The method is expecially applicable to differentiate between the naturally occuring choline esters since they contain various functional groups which are infrared absorbing. Infrared also provides a quick and reliable method for the identification of the strong absorption pattern of the ester linkage even in trace amounts.

STRUCTURE ACTIVITY RELATIONSHIP OF A SERIES OF COMPOUNDS RELATED TO 4-(m-Chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium chloride (McN-A-343). John Yelnosky* and Adolph P. Roszkowski, McNeil Laboratories, Inc., Fort Washington, Pa.

It has recently been shown (Roszkowski, JPET 132: 156-170, 1961) that the compound McN-A-343 causes an increase in blood pressure in anesthetized cats and dogs which is due to stimulation of sympathetic ganglia. However, this compound differs from ganglionic stimulants like nicotine and DMPP in that its action is not antagonized by well-known ganglionic blocking drugs (e.g., hexamethonium) but is readily antagonized for long periods of time by atropine and other anticholinergic agents. This study was undertaken to establish a structure-activity relationship for this particular type of activity in related compounds. Some of the findings to be reported are 1) a quaternary nitrogen is essential for ganglionic stimulant activity of this type, 2) saturation of the triple bond causes a decrease in pressor activity, 3) substitution of N-ethyl groups for the N-methyl groups results in an agent that blocks the ganglionic effect of the parent compound, and 4) substitution of the chlorinated phenyl group by hydrogen produced a compound with peripheral cholinomimetic actions.

GANGLIONIC STIMULATION AND BLOCKADE PRODUCED BY INDOLE COMPOUNDS. Laszlo Gyermek and Elliot Bindler.* Geigy Research Laboratories, Ardsley, N. Y.

A series of 16 indole 3-alkylamine derivatives have been studied in the inferior mesenteric ganglion preparation of the cat (Herr and Gyermek: J. Pharmacol. 129: 338, 1960). Compounds which caused ganglionic stimulation were, in order of potency: 5-HT, bufotenine and N,N-dimethyltryptamine. Tryptamine only occasionally produced stimulation in relatively large doses. The stimulant action of these amines is different from cholinergic ganglionic stimulation. 5-hydroxy-3-indoleacetamidine and 3-indoleacetamidine primarily produced ganglionic blockade which was specific for 5-HT. Both compounds were far more potent and selective than the commonly known 5-HT antagonists (Bindler and Gyermek: Fed. Proc. 20:319,1961). The other indole compounds were found to be weak and/or nonspecific blocking agents for 5-HT. The chemical structural characteristics necessary for eliciting a 5-HT type stimulant action on autonomic ganglia are outlined.

AUTONOMIC ALTERATION OF UNEXPECTED PRESSOR EFFECTS OF N-BENZYL-3-PYRROLIDYL ACETATE·CH$_3$Br (AHR-602). B. Franko,* J. Wardy and R. Alphin.* A. H. Robins Biol. Res. Labs., Richmond, Va.

AHR-602 which bears structural similarity to methacholine was found to produce unexpected pressor effects in dogs, cats, and rats. Blood pressure effects were not always consistent from animal to animal being depressor, biphasic, or pressor in nature. The pressor response could uniformly be unmasked or potentiated with DMPP blocking doses of hexamethonium or TEA. Spinal section at C-2 did not alter the pressor response. Adrenalectomy reduced it slightly while thoracic postganglionic sympathectomy practically abolished it. Pressor activity was abolished with dibenamine, azapetine, TM-10, guanethidine and reserpine. Apparent depolarization of the ganglia with TMA also abolished the response. The most effective antagonist appears to be atropine which inhibited the pressor response at a dose of 5 mcg./kg. IV. AHR-602 had essentially no effect on the isolated guinea pig ileum or tracheal chain, the rabbit aortic strip, the isolated rat uterus, or the turtle heart in situ. This suggests that AHR-602 acts at sympathetic ganglionic sites other than those involved with acetylcholine. The pressor activity of AHR-602 appears to be similar to that described for various drugs by Trendelenburg (Fed. Proc. 18: 1001, 1959) and for McN-A-343 by Roszkowski (J. Pharmacol. Exp. Therap. 132: 156, 1961).

THE INHIBITORY EFFECT OF l-EPINEPHRINE ON PURIFIED, CONCENTRATED HUMAN PLASMA CHOLINESTERASE. E. K. Zsigmond,* V. M. Foldes* and F. F. Foldes. Dept. of Anes., Mercy Hospital and Univ. of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

It was reported earlier (Erdös et al, Abstracts of Communications, XX. Int. Physiol. Cong., p. 274, Brussels, Belgium, 1956) that indolalkylamines inhibited human plasma cholinesterase (ChE). These findings prompted the investigation of the inhibitory effect of l-epinephrine and related compounds on the hydrolysis of ACh by human plasma and red cell ChE by Ammon's modification of Warburg's manometric method. l-Epinephrine was found to have a significant inhibitory effect ($I_{50} = 2.0 \times 10^{-5}$M) on purified and concentrated human plasma ChE (Cholase). When, instead of Cholase, heparinized human plasma was used, epinephrine, probably because of its rapid breakdown in plasma, had no anti-ChE activity. The I_{50} value of adrenochrome with Cholase was 1.2×10^{-3}M. l-Norepinephrine had no significant inhibitory effect. The I_{50} value of l-epinephrine for the hydrolysis of ACh by red cell ChE was 2.2×10^{-2}M. It is possible that the facilitating effect of epinephrine on the preganglionic transmission of the superior cervical ganglion of the cat (Bülbring, E., J. Physiol. (Lond), 103:55, 1955) is due to the anti-ChE effect of this compound.

ATTEMPTS TO REVEAL A HUMORAL FACTOR IN VAGOTOMY-INDUCED PULMONARY EDEMA. L.E. McCarthy*, R.H. Rech*#, and H.L. Borison.
Dept. Pharmacol., Univ. Utah Coll. Med., Salt Lake City.

Repeated efforts to produce chronic parabiosis in guinea pigs proved futile. Accordingly, bilateral vagotomy was performed in animals that had been joined by abdominal anastomosis for 18-24 hrs. In 5 pairs in which both mates were vagotomized, lung edema was found in every animal that succumbed (all within 9 hrs) and in 4 of the 5 mates that were killed at the corresponding times. In 5 pairs in which one mate was vagotomized, edema still developed in every vagotomized animal (although 2 pairs survived for 10 and 12 hrs, resp.), and 4 of the 5 non-vagotomized mates presented no evidence of edema. Lung edema was not found in 2 pairs subjected to sham vagotomy and allowed to survive longer than 10 hrs. Thus, results of acute parabiosis failed to support the hypothesis of a humoral factor in vagotomy-induced pulmonary edema. Chronic parabiosis was accomplished in rats, but vagotomy-induced lung edema could not be produced regularly in this species. To probe other indirect mechanisms, 6 guinea pigs were vagotomized 18-24 hrs after nephrectomy. Severe lung edema resulted while mean survival time was shortened. Na salicylate (300-750 mg/kg i.p.) also did not prevent lung edema after vagotomy. The dose of 1000 mg/kg produced lesions by itself. (Supported by PHS Grant B-491.) #NIH Postdoctoral Fellow HF-9406.

CARDIOVASCULAR PHARMACOLOGY III
Todd West

THE EFFECT OF l-EPINEPHRINE AND l-NOREPINEPHRINE ON CAT PAPILLARY MUSCLES. Dai H. Yu* and Kwang S. Lee. State Univ. of N.Y., Downstate Medical Center, Brooklyn, N.Y.

The relationship between the metabolic and inotropic actions of epinephrine and norepinephrine has been studied. For this purpose, the oxygen consumption, the contractility and the content of energy-rich phosphate compounds of cat heart papillary muscles were measured simultaneously using the method described previously (Lee et al, J. Pharmacol, 132; 139, 1961). The oxygen consumption and the contractile tension increased concomitantly following the addition of these drugs. The change of mechanical efficiency following the administration of these agents depend on the state of muscle at the time of administration. Thus, when muscles were fresh and the contractility was unimpaired, the improvement of mechanical efficiency was much less than that seen with "hypodynamic" muscles. Both epinephrine and norepinephrine do not appear to increase the oxygen consumption of non-contracting muscles. The content of ATP, ADP, AMP, IP and creatine phosphate did not change significantly following the addition of these agents. DCI blocked completely both the metabolic and inotropic effects of these amines. (Supported by grant #H-2875, USPHS).

EFFECTS OF SUCCINATE AND ITS HYDROXY DERIVATIVES ON MYOCARDIAL TENSION. G. Alan Robison,* T.D. Darby, and F.W. Schueler. Dept. of Pharmacology, Tulane U. School of Medicine, New Orleans, Louisiana.

The hydroxy derivatives have variable inotropic effects. L(+)-Tartaric acid has been found to be capable of causing a marked and relatively prolonged positive inotropic effect in the isolated perfused rabbit heart. In the anesthetized (pentobarbital) dog, tartrate exerts a negative inotropic effect (as do also malate and malonate), whereas succinate has a positive effect. It has been suggested that muscle contraction depends on two reactions: (1) the combination of energy and the contractile proteins and (2) the release of this energy and the reaction of the proteins. In the present studies, measurable changes in heart size accompanied the inotropic responses. Measurements of tension at a fixed length suggested a diastolic alteration in the length-tension relationship of the muscle during the inotropic response. Currently under investigation are (1) the relationship between the pharmacological action of these agents and their degree of ionization, and (2) the possibility of a physiologic role for tartaric acid.

EVIDENCE SUPPORTING A CURRENT THEORY OF MUSCLE CONTRACTION. T. D. Darby, and J. J. Walsh*. Dept. of Medicine and Pharmacology, Tulane U. New Orleans, La.

It has been suggested that muscle contraction depends on two reactions: (1) a combination of energy and the contractile proteins and (2) the utilization of energy and the reaction of actin and myosin. The first reaction is thought to occur in diastole and could have an effect on the length-tension relationship of cardiac muscle. The second is believed to be related to the isometric tension developed during systole and to the free energy change. The present studies were conducted in anesthetized (pentobarbital) dogs. A modification of the strain gauge lever system was used to measure muscle segment length and tension. Changes in tonus were observed in the insitu ventricular myocardium in response to the catecholamines, calcium, pentobarbital, salyrganic acid, hypercapnia, hypoxia, and anoxia. The changes in end-diastolic length-tension relationship could be opposite to that expected from the inotropic response. This suggest that drugs can separately influence the two proposed reactions associated with muscle activity.

UNCOUPLING OF MYOCARDIAL ELECTRICAL ACTIVITY AND CONTRACTION IN DOGS. Charles H. Ellis and Honora N. Miller.* Wellcome Research Laboratories, Tuckahoe, New York.

Methoxamine hydrochloride causes pulsus alternans in dogs, usually without modifying the ECG. The absence of electrical changes suggests interference with the contractile process or with activation links between depolarization of the cell membrane and the contractile process. Contraction of myocardial fibers is believed to be activated by entry of Ca^{++} into the cell from extracellular sites. It is postulated that drug-induced pulsus alternans is related to modification in the transfer of Ca^{++} into the fiber. Depletion of extracellular Ca^{++} should exacerbate the condition. Na_2EDTA was used to chelate Ca^{++}, and in the dosage used had little direct myocardial effect. Only a slight potentiation of methoxamine resulted. When methoxamine was given before the chelating agent, however, Na_2EDTA caused profound failure in myocardial contractility without modifying the ECG. Monophasic action potentials were not changed even with pulse deficit. Uncoupling of the contractile process from membrane depolarization apparently occurs. The disodium salt of diethylenetriamine penta acetate showed similar activity. The effects were relieved by methamphetamine, ephedrine and norepinephrine; they could be prevented by pretreatment with methamphetamine, ephedrine, pseudoephedrine or digoxin.

A G-STROPHANTHIN SENSITIVE-Na+K ACTIVATED ATPase IN RABBIT BRAIN, CARDIAC AND STRIATED MUSCLES. *Ralph J. Cazort and Joseph V. Auditore.* Departments of Pharmacology, Meharry Medical College and Vanderbilt Medical School, Nashville, Tennessee.*

The influence of Na^+, K^+, Mg^{++} and g-strophanthin in various combinations on the ATPase activity in rabbit brain, cardiac and striated muscles have been investigated. An ATPase in these various tissues has been uncovered that is highly dependent on the relative concentrations of Mg^{++}, Na^+ and K^+. Magnesium is an absolute requirement for the enzyme activity. With Mg^{++} in the system Na^+ will stimulate brain ATPase activity while K^+ apparently will not. However, the addition of Na^+ plus K^+ in the presence of Mg^{++} markedly increases enzymatic activity. A similar $Na^+ + K^+$ dependent enzymatic activity has been found in the cardiac and striated muscles of the rabbit. The $Na^+ + K^+$ activated component is readily inhibited by low concentrations of g-strophanthin while that activity due to magnesium ions is not affected.

EFFECT OF ALDOSTERONE ON ACTIONS OF OUABAIN ON ISOLATED CARDIAC MUSCLE. Joseph V. Levy* and Victor Richards* Research Labs., Presbyterian Medical Center, San Francisco, Calif.

Aldosterone(ALDO) is alleged to stimulate active Na-K transport across cell membranes. Ouabain, on the other hand, is well known to inhibit active transport of these ions in a variety of tissues, including the heart. Experiments were performed to determine whether the actions of ouabain on driven, isolated rabbit atrial preparations could be antagonized or otherwise modified by the presence of ALDO. With constant perfusion, ouabain(1.7×10^{-6}M) alone produces a marked decrease in electrical excitability(EX), lengthening of functional refractory period(FRP), decreased contractile tension(DCT), and contracture. Simultaneous perfusion of 1.7×10^{-6}M d,l-ALDO (Ciba) and ouabain was found to delay slightly the onset of DCT and contracture. Changes in FRP and EX were similar to those seen with ouabain alone. ALDO alone produces a slight DCT, but no other consistent changes compared to untreated controls. Attempts to reverse ouabain effects by washing with ALDO produced changes similar to those seen with control Ringer's wash. While these experiments do not exclude the possibility of more subtle effects on cation fluxes, there is no clear evidence of antagonism or reversal of glycoside effects by ALDO with the concentrations and conditions employed. (Suppt. by NIH grant H-6027 and San Mateo County Heart Assoc.).

CALCIUM REVERSAL OF ANTIFIBRILLATORY DRUGS. P. E. Leveque*, J. Sohanno*, and C. A. Hufnagel*, Depts. of Pharmacology and Surgery, Georgetown U. Schools of Medicine and Dentistry, Washington, D. C.

The antagonism between Ca and K is well known. This is especially true in digitalis-induced cardiac arrhythmias which are exacerbated by Ca and relieved by K. Experiments were performed to ascertain the reciprocal relationship between Ca and K in experimental auricular fibrillation induced with ACh (0.5 mg/kg or less). Although Ca "reverses" the action of certain antifibrillatory drugs (Antazoline, observed by J. S., and Diphenhydramine), acutely induced hypercalcemia ($CaCl_2$ 10%, about 4 ml), unlike hypokalmia (induced with insulin and glucose), does not routinely cause increased incidence to auricular fibrillation with ACh. ACh, given together with or immediately followingCa, usually produces AV block (ACh-induced) and PVC (Ca induced?). Slightly higher doses of Ca (20%) in this combination kill the dogs by ventricular fibrillation (Ca-induced). (supported by Grant H-5099, USPHS.)

EFFECT OF ANGIOTENSIN (HYPERTENSIN) ON VENTRICULAR CONTRACTILE FORCE. J. L. Butterfield* and J. A. Richardson, Medical College of South Carolina, Charleston.

In anesthetized, open-chest, bilaterally vagotomized dogs, hypertensin in equipressor doses was less effective than levarterenol but more effective than methoxamine in producing increments in ventricular contractile force. With single injections, positive inotropism appeared after pressor action was well established. A high incidence of arrhythmias was noted. Generally similar responses were noted after ganglionic blocking agents or total preganglionic sympathetic blockade.
Supported by grants from National Heart Institute and South Carolina Heart Association.

INCREASE OF CORONARY FLOW PRODUCED BY BRADYKININ ON IN VITRO MAMMALIAN HEARTS. Abílio Antonio* and M. Rocha e Silva. Department of Pharmacology, Faculty of Medicine, U.S.P., Ribeirão Prêto, E. São Paulo, Brazil.

It has been shown that bradykinin is one of the most powerful vasodilating substances to be found in the body, with a predominant action upon peripheral small vessels. When tested upon the isolated mammalian heart using the Langendorff's method, bradykinin was found to produce considerable increase in coronary flow, when small fractions of microgram of the synthetic material (from Sandoz, Basel) was perfused through the guinea pig's, rabbit's, cat's and dog's heart in a modified Tyrode solution. The guinea pig's heart was so far the most sensitive, reacting to final concentrations of the order of 10^{-9}. Besides this increase of coronary flow, bradykinin had small or questionable effects upon cardiac contractility, contrasting sharply with those produced by epinephrine. Concentrations of the latter which already produced sharp positive inotropic and chronotropic effects had only slight effect upon the coronary flow, after a latent interval. The effects produced by bradykinin upon the coronary flow were immediate and conspicuous, without very much change in rhythm or amplitude of the beat.

TAURINE LEVELS IN HEART TISSUE OF VARIOUS SPECIES. J. J. Kocsis and V. J. Kostos*. Dept. of Pharmacology, Jefferson Med. Coll., Philadelphia, Pa.

Awapara found that among several tissues in 6 species the heart had the highest taurine levels. To elucidate the role of taurine in the heart we determined taurine levels in the hearts of various species and in various parts of the heart. In 3 dogs despite marked variations in taurine levels in both auricles (1050-5287 mcg/g) and ventricles (595-1824 mcg/g), the ventricular/auricular (V/A) ratio was relatively constant and served to distinguish between right and left hearts, V/A ratios in the left heart being 0.36, 0.34 and 0.43 and that in the right heart 0.42, 0.44 and 0.65, respectively. In 3 rabbits, on the other hand, taurine in the ventricles was 4 x that of the auricles (825 mcg/g). In beef, rat, cat, human and guinea pig hearts the V/A ratios were between those of the rabbit and the dog. High doses of 2 cardioactive drugs changed taurine levels in rat hearts. Twenty mins after ouabain (100 mg/kg) V/A ratios in the hearts of treated rats were lower than that of controls. Although 48 hrs after giving isoproterenol (85 mg/kg), heart weight increased 25-30%, heart taurine levels and urinary taurine excretion did not change consistently. Further studies of these drug-induced changes are in progress. (Supported by U.S.P.H.S. CY-3349)

HEMODYNAMIC EFFECTS OF ISOSORBIDE DINITRATE. S.Afonso*, G.G.Rowe, C.A.Castillo*, W.C.Lowe* and C.W.Crumpton. Cardiovascular Res.Lab., Dept.of Med., U.of Wis., Madison, Wis.

10 anesthetized mongrel dogs were studied. A single I.V. dose of 0.45 mg./kg. was given to 5 dogs (Group I) while the other 5 (Group II) received a continuous I.V. infusion at a rate of 0.1 mg./kg./min. Observations were made before and after or during administration of the drug. Mean right atrial ($p< 0.01$), pulmonary arterial ($p< 0.001$) blood pressure, right ($p< 0.001$) and left ventricular work ($p< 0.02$), stroke volume ($p< 0.001$), arterial ($p< 0.01$) and mixed venous CO_2 contents ($p< 0.001$), coronary sinus O_2 and CO_2 contents and index of cardiac efficiency ($p< 0.02$) decreased significantly. Heart rate ($p< 0.01$), body R.Q. ($p< 0.01$), cardiac R.Q. ($p< 0.01$) and arterial-coronary sinus O_2 difference ($p< 0.01$) increased significantly. In the Group I dogs significant increases occurred in mean systemic arterial blood pressure ($p< 0.02$) and total peripheral resistance ($p< 0.02$) and a decrease in cardiac output ($p< 0.05$). Group II dogs showed a significant decrease in mean systemic arterial blood pressure ($p< 0.02$). Coronary blood flow and coronary vascular resistance did not change significantly. Under the conditions of this study no changes attributable to a vasodilator action were observed.

CARDIOVASCULAR PHARMACOLOGY III

A THREE YEAR STUDY OF TRIPARANOL. Philip Lisan*, Wilbur Oaks*, and John Moyer, Hahnemann Medical College and Hosp. Phila. Pa.

This is a clinical study of 21 patients with coronary artery disease who were followed continuously on triparanol for periods of 24 to 36 months. There was a significant and persistent fall in cholesterol (38mg.%) with a $P<0.001$, in 85% (18) of these patients during the 2 to 3 year study. Triparanol inhibits cholesterol synthesis. There was no clinical evidence of toxicity. Liver function studies showed no impairment of function (bromosulfathalein) even at the 3 year period. Renal and hematological parameters remained unchanged and within normal limits. Other fat studies such as serum triglycerides, unesterified fatty acids and lipoproteins could not be correlated with the reduction in cholesterol. There were 23 patients in the original series but 2 patients died of coronary thrombosis with myocardial infarction at 12 and 14 months. Only 1 patient (of 21) had another coronary thrombosis, also at 12 months, but survived and now has reached 24 months. Subjectively the patients had dimunition in frequency and severity of angina pectoris and intermittent claudication.

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A MUSCLE-INHIBITORY SUBSTANCE OF HUMAN PLASMA. Ted S.Konop* and W.Kalow, Department of Pharmacology, University of Toronto, Toronto, Canada.

Dialysed human plasma has a weak curare-like effect on the isolated frog rectus muscle. Precipitation of plasma proteins with trichloroacetic acid leaves the responsible plasma constituent in the supernatant. On dialysing the supernatant, most of the active material remains in the dialysing bag. The material can be further purified by adsorption on an aluminum oxide column at pH 8.5 and elution by 0.5 M acetic acid. In neutral solution, the material can withstand boiling for an hour but the activity disappears after boiling in normal HCl or NaOH. Incubation with trypsin does not cause inactivation. The material is soluble in methanol. For bioassay, the frog rectus needs to be exposed to the active agent for one minute prior to the addition of acetylcholine. Dose-effect curves suggest that the agent acts by competitive inhibition of acetylcholine. The agent inhibits guinea pig ileum to a lesser extent than it does frog muscle.

(Supported by a grant from the Banting Research Foundation).

CURARE-LIKE ACTIVITY OF HIGH MOLECULAR WEIGHT POLYPROPYLENE GLYCOL ADDUCTS. Leslie P. McCarty,* Barbara L. Ruffe* and Maynard B. Chenoweth. The Dow Chemical Company, Midland, Michigan.

Bis-diethylenetriamine adducts (PG-DETA) have been synthesized from polypropylene glycols of various molecular weights. These compounds show pharmacological properties similar to those of curare. Neuromuscular blockade was produced with a dose of 1 mg./kg. in the cat gastrocnemius preparation and a concentration of 10^{-5} g./ml. in the isolated rat phrenic nerve-diaphragm preparation. This effect can be somewhat antagonized by administering appropriate quantities of edrophonium. Repetitive doses of PG-DETA caused a stepwise reduction in blood pressure and a dose of 2 mg./kg. blocked the ganglion stimulating effect of nicotine or acetylcholine. The molecular weight of the glycol chain in these adducts influences the pharmacological activity; i.e., 400, moderate activity; 1200, high activity; and 2000, weak activity.

THE NEUROMYAL BLOCKING ACTION OF THE MONOAMINE OXIDASE INHIBITORS. A. Ammann* and E.G. Anderson. Dept. of Pharmacol., Seton Hall Coll. of Med., Jersey City, N.J.

It has been previously reported that several monoamine oxidase (MAO) inhibitors will block neuromyal transmission in the isolated frog sartorious muscle preparation (Anderson, The Pharmacologist 1:82, 1959). Further investigation has been carried out using the isolated rat phrenic-nerve diaphragm preparation. Several structurally unrelated MAO inhibitors such as iproniazid, phenylcyclopropylamine (Parnate), MO 911, and harmaline have been found to block neuromyal transmission in concentrations ranging from $1x10^{-3}$ to $5x10^{-4}$M. In each case the concentration of drug required to block transmission was much lower than the concentration which blocked phrenic nerve conduction. The MAO inhibitors also blocked the chronic denervated hemi-diaphragm's response to acetylcholine.

EFFECTS OF RYANODINE ON RABBIT MUSCLE FRACTIONS. Alan S. Fairhurst* and Donald J. Jenden. Dept. Pharmacology, UCLA Medical Center, Los Angeles 24, California.

The effect of the alkaloid ryanodine has been studied on crude extracts and granule fractions of rabbit skeletal muscle associated with the process of relaxation. The formation of relaxing factor has been measured by its inhibitory effect on myofibrillar ATPase, following the H^+ liberation at constant pH. Ryanodine decreases the inhibition of myofibrillar ATPase produced by the relaxing factor system, suggesting that a site of action of the alkaloid lies within this system. Measurements have also been made of the increased ATP splitting produced by the addition of Ca^{++} to the granules in the absence of myofibrils (cf. Hasselbach and Makinose, Biochem. Z., 333 518 (1961)). In this system ryanodine does not affect the rate of ATP utilization, but does increase the amount of ATP split when a given quantity of Ca^{++} is taken up by the granules. The efficiency of Ca^{++} uptake is therefore decreased. The effect of ryanodine is more marked as the Ca^{++} load is increased, and when the Ca^{++} additions are raised to near saturation levels for the granules, effects can be demonstrated with 10^{-6} M ryanodine. It is suggested that the muscular rigor produced by ryanodine may be the result of interference with the relaxing function of these granules.

PHARMACOLOGICAL PROPERTIES OF OXETHAZAINE: A POTENT LOCAL ANESTHETIC. Jerome M. Glassman, George M. Hudyma*, Felix Rauzzino* and Joseph Seifter. Wyeth Laboratories, Inc., Basic Medical Sciences Research Division, Radnor, Pa.

Oxethazaine, N,N-bis-(N-methyl-N-phenyl-t-butylacetamide)-β-hydroxyethylamine HCl, combines adrenergic and cholinergic moieties in the molecule. This highly potent local anesthetic has greater effectiveness by corneal application or canthus infiltration than either dibucaine, cocaine, lidocaine or procaine and is 10, 500, 2,000, 4,000 times more potent respectively. It is unique in that its salts ionize poorly even at low pH. Whereas lidocaine and procaine have relatively negligible activity when applied to the eye in highly acid solution, oxethazaine is very effective even at pH 1; thus it easily penetrates lipids of nerve sheaths to effect adequate anesthesia of long duration. It is, therefore, useful for controlling pain of peptic ulcer, gastritis and esophagitis. Oral administration is safe and continuous feeding to dogs and rats for 7 mos. has little effect on organs, tissues or peripheral blood. Large doses may be anorexogenic. It is a potent spasmolytic agent when applied to the smooth muscle of the rabbit jejunum or constricted vessels of the isolated ear. It is also weakly antihistaminic. Intratracheal or intravenous administration is toxic: death is due to either paralysis of the bronchioles or myocardial depression, respectively.

TRACER STUDIES ON OXETHAZAINE. Robert Wiser* and Joseph Seifter Wyeth Laboratories, Inc., Basic Medical Sciences Research Division, Radnor, Pa.

Oxethazaine, N,N-bis-(N-methyl-N-phenyl-t-butylacetamide)-β-hydroxyethylamine hydrochloride is a highly potent local anesthetic currently in clinical use for the treatment of esophagitis, gastritis, and peptic ulcer. For metabolism and distribution studies, this substance was synthesized with a C^{14} label in both carbon atoms of the ethanolamine moiety. Upon oral administration of the drug in rats, radioactivity appears in the respiratory carbon dioxide within 30 minutes, and in 28 hours 20% of the administered activity is eliminated in this form. Urinary excretion accounts for 18% of the dose in 72 hours; another 13% is found in the feces in the same time interval. In a study of the pH dependence of the partition of oxethazaine between water and carbon tetrachloride, the 50-50 distribution point was found to be at pH 2.8. For dibucaine and procaine the equivalent pH values were 5.1 and 7.8 respectively. Oxethazaine hydrochloride is soluble in chloroform to the extent of 1.1 gm/ml, and is completely extracted by chloroform from water at pH 1.0. This evidence of extremely weak basicity and organic solubility can be correlated with the drug's efficacy at low pH.

THE NEUROMUSCULAR EFFECTS OF DI-ALLYL-NOR-TOXIFERINE IN CONSCIOUS AND ANESTHETIZED SUBJECTS. I. M. Brown*, F. F. Foldes, J. N. Lunn* and J. Moore*. Dept. of Anes., Mercy Hospital and Univ. of Pgh. School of Medicine, Pittsburgh, Pennsylvania

Di-allyl-nor-toxiferine (RO4-3816) is a synthetic, non-depolarizing neuromuscular blocking agent. The intravenous injection of 60 γ/kg to 10 healthy, conscious subjects caused a 7.3 ± 2.7% decrease of vital capacity and 76.2% decrease of grip strength. Maximum effect developed within 5 minutes. Grip strength returned to control within 15 minutes and to 90% within 30 minutes. The intravenous administration of 125 γ/kg RO4-3816 to 10 lightly anesthetized patients caused a 42.6 ± 4.1% depression of respiratory tidal volume within 3 minutes. Tidal volume returned to control within 20 minutes. Under similar circumstances, a 200 γ/kg dose caused apnea in 5 out of 10 subjects, a mean decrease of the respiratory tidal volumes of 90.9 ± 3.1%. Tidal volumes returned to control within 25 minutes. In 30 patients, RO4-3816 was used for the maintenance of abdominal relaxation during surgery. An initial dose of 125 γ/kg followed by 30 γ/kg fractional doses, 20 minutes apart, produced satisfactory relaxation without complete paralysis of the respiratory muscles in most cases.

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PRACTICE AS A VARIABLE IN ALTERING THE EFFECTS OF DRUGS. Conan Kornetsky and Joy Dawson.* Dept. of Pharm. & Exptl. Therap., Boston Univ. School of Medicine, Boston, Mass.

The present report deals with the role of practice in determining the behavioral effects of drugs. Male albino rats, maintained at 80% of their ad libitum weight, were trained on a fixed ratio schedule of 50 responses per reinforcement (a food pellet). Animals were given practice in the experimental chamber one hour a day, seven days a week. After stable response rates were obtained all animals were injected intraperitoneally with pentobarbital, d-amphetamine and water on separate days. Animals were tested a number of times after various doses of both drugs over a period of several months. On days when no drugs were given, animals still received practice in the experimental chamber. The results indicated that low doses of both drugs early in the sequence of the animals' experimental experience had significantly greater effect on rate of lever pressing than the same doses late in the sequence of the animals' experimental experience. The effects of relatively high doses of the two drugs were not altered by the amount of practice that the animals had prior to drug administration. The failure of practice to significantly alter the effects of the higher doses suggests that tolerance to the drug per se contributes very little to these results. (Supported by NIH grants MY 3312 (C2) and SF-310-C-S.)

IMPAIRMENT OF CARDIAC AND MOTOR CONDITIONAL REFLEXES AFTER ENCEPHALOPATHY PRODUCED BY ANTI-DOG BRAIN SERUM. Clara H. Williams* and W. Horsley Gantt. VA Hospital, Perry Point, Md.

We showed that an encephalopathy (8-24 hrs. duration) resulted when two dogs were given i.v. or subarachnoid injections of rabbit antiserum to dog brain. These dogs had previously developed strong cardiac and 100% motor conditional reflexes (CR) to an excitatory tone of 500 cycles reenforced by faradic shock and gave no response to an inhibitory tone of 1000 cycles with no shock. On the days when the encephalopathy occurred both motor and cardiac CRs were diminished. After several encephalopathies the motor and cardiac CRs to the excitatory tone gradually decreased and finally disappeared. Differentiation between excitatory and inhibitory tones was not impaired. Normal rabbit serum produced neither an encephalopathy nor any CR changes in these dogs. Brain sections will be shown. We conclude that brain damage resulted from repeated injections of antidog-brain serum and this cerebral pathology is reflected earlier in the delicate CR function since gross neurological and behavioral findings were not apparent. This parallels what we have found in anoxia, postconvulsive states and vitamin deficiencies.

BEHAVIORAL AND BIOCHEMICAL ACTIVITY OF A NEW SERIES OF BENZOQUINOLIZINE DERIVATIVES. K. F. Finger*, A. Weissman* and J. R. Tretter*. Chas. Pfizer & Co., Inc., Groton, Conn.

A series of substituted 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzoquinolizines has been synthesized and investigated for behavioral depressant properties and release of central amines. Structural changes in the 2 and 3 positions produced pronounced variations in biological activity. P-2565, one epimer of 2-hydroxy-3-(N,N-diethylcarbamyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzoquinolizine, produced sedation, ptosis, lacrimation and salivation in mice at 10 mg/kg I.V., and above and at these doses it released brain serotonin and norepinephrine. The other epimer, P-2518, was far less active in producing sedation and reserpine-like symptoms in mice, and failed to release brain amines. Similarly, P-2565 was at least 10 times more potent than P-2518 in rats in depressing conditioned nondiscriminated avoidance behavior. Acetylation of the 2-hydroxy group of P-2565 yielded a compound, P-2647, which was at least as potent as P-2565 in disrupting conditioned nondiscriminated avoidance in rats and monkeys. Unlike P-2565, however, P-2647 failed to release central amines, and it was far less active than P-2565 in producing sedation, ptosis, lacrimation and salivation.

DISRUPTION OF THE CONDITIONED AVOIDANCE RESPONSE OF TRAINED RATS WITH 5-METHOXY-N:N-DIMETHYLTRYPTAMINE. P. K. Gessner.* Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Both a hydroxyindole-O-methylase and an enzyme capable of N-methylating indoleethylamines are known to exist in the mammalian organism. The action of these enzymes on serotonin would give rise to 5-methoxy-N:N-dimethyltryptamine. The ability of this compound to disrupt the conditioned avoidance response, on i.p. injection, was compared to that of N:N-dimethyl and N:N-diethyl tryptamines, bufotenine, 5-benzoxy-N:N-dimethyltryptamine, LSD-25 and water. The tests were made using 30 rats per compound and a shuttle box with a conditioned light stimulus and a 2 milliampere, 25 volt unconditioned electric shock stimulus in 25 second cycles. 5-Methoxy-N:N-dimethytryptamine (19 μM/kg) was the most effective tryptamine tested both in the magnitude of the effect and in the rapidity of onset, the disruption reaching a median value in 1.8 min. LSD-25 was similarly active at a lower dose level (6 μM/kg), however the median value was reached only after 6.3 min. At the higher dose of 25 μM/kg the other tryptamines were less effective, N:N-dimethyl and N:N-diethyl tryptamines being however more effective than 5-benzoxy-N:N-dimethyltryptamine and bufotenine. It is concluded that 5-methoxy-N:N-dimethyltryptamine is very effective in disrupting the conditioned avoidance response in rats.

THE EFFECTS OF SEVERAL DRUGS ON GROSS MOTOR ACTIVITY OF MICE EXPOSED TO ETHER. Max A. Heinrich, Jr. and Donal M. Moe*. Dept. Pharmacology, North Dakota State Univ., Fargo.

Pretreatment with low doses of several depressants prolonged treadmill-type running of mice exposed to ether vapor (Fed. Proc. 16: 306, 1957). Less excitement was observed in treated mice which could decrease respiratory exchange and the rate of ether absorption. This hypothesis was tested by recording gross motor activity of mice exposed individually to ether in a 3.1 l chamber. A stylus was attached to a 9 cm disk cemented to the 15 cm rubber diaphragm which formed the floor of the chamber. The stylus completed an electrical circuit advancing a digital counter when a mouse jumped within the chamber. Normal walking was not recorded. Jumping produced during exposure to 8.4% ether was significantly decreased ($P < 0.05$) by subcutaneous pretreatment with 0.5 mg/kg pentobarbital sodium, 0.25 mg/kg chlorpromazine hydrochloride or 20 mg/kg amphetamine sulfate administered 1/2 hour before ether exposure and by 0.05 mg/kg reserpine injected 24 hours prior to testing. These findings support the assumption that depressants decrease gross motor activity during ether exposure. The data suggest the possibility that this technic may provide another method with which to detect depressant potentialities of a drug.

DIFFERENTIAL TOLERANCE DEVELOPMENT TO THE AVOIDANCE AND LOCOMOTOR SUPPRESSANT ACTIONS OF PERPHENAZINE AND CHLORPROMAZINE. S. Irwin. Dept. of Neuropharmacology, Schering Corp., Bloomfield, N.J.

In male Charles River rats (CD), tolerance and cross tolerance have been observed to develop to the avoidance (hurdle-jump) but not to the locomotor (revolving treadwheel) suppressant actions of equivalent doses of perphenazine (0.3 mg/kg) or chlorpromazine (3.0 mg/kg) i.p. After a single dose of chlorpromazine, avoidance responses of animals tested 1, 3 and 7 days later were approximately 50%, 65% and 80% of the avoidance failures observed on the first day of dosing. Administered chronically once daily for 26 days, almost complete tolerance developed within 14 days to the avoidance effects of chlorpromazine, and the animals were still 30% tolerant after 31 days of withdrawal. Only partial tolerance (approximately 45%) developed to the avoidance suppressant action of perphenazine during the same period, and the animals regained their original sensitivity to drug more rapidly (e.g., only 15% tolerance after 10 days of withdrawal). Of particular interest was the complete absence of tolerance development to the locomotor suppressant actions of both drugs during their chronic daily administration, a finding opposite of that reported by Boyd after very much larger doses of chlorpromazine (J.P.E.T., 128: 75, 1960).

COMPARISON OF SOME PHARMACOLOGICAL PROPERTIES OF IMIPRAMINE, AMITRIPTYLINE, PROMAZINE AND THEIR DESMETHYL DERIVATIVES. E. B. Sigg, L. Gyermek and L. Soffer.* Geigy Research Laboratories, Ardsley, N. Y.

Imipramine and, to a lesser degree, amitriptyline potentiated the action of 5-HT and norepinephrine on the normal cat nictitating membrane preparation. The corresponding desmethyl derivatives are predominantly norepinephrine potentiators, desmethyl imipramine being more potent than desmethyl amitriptyline. Promazine and desmethyl promazine were weak blocking agents of 5-HT and norepinephrine. The antagonism of reserpine sedation in mice was quantitatively determined in a modified locomotor activity test after i.v. administration of the drugs. It was found that promazine and desmethyl promazine antagonized reserpine sedation as well as the antidepressant compounds and their desmethyl derivatives. The potentiating and blocking effects of these amines to 5-HT and norepinephrine on the nictitating membrane are thought to be proportional to their antidepressant and tranquilizing action. No correlation was found between antidepressant potency and antagonism to reserpine induced sedation.

POTENTIATION OF METHYLPHENIDATE BY IMIPRAMINE, AMITRIPTYLINE AND THEIR DESMETHYL ANALOGUES. R. T. Hill*, I. Koosis*, M. W. Minor* and E. B. Sigg, Geigy Research Laboratories, Ardsley, N. Y.

On an operant behavior schedule (crf drl) rats were required to space bar presses by at least 18 seconds to obtain a small cup of milk. The effect of methylphenidate is a shortening of interresponse times. Imipramine, amitriptyline and their desmethyl derivatives do not have this effect per se, but after pretreatment with these agents at a dose (10 mg/kg per os) which has no appreciable influence on timing behavior, the effect of methylphenidate, 5 mg/kg i.p., is enhanced. These observations are in accord with the imipramine potentiation of amphetamine effects on avoidance behavior reported by Carlton (The Pharmacologist, 2:70, 1960) and on hypothalamic self-stimulation reported by Stein and Seifter (Fed. Proc., 20:395, 1961). Since the central component of methylphenidate is more predominant than that of amphetamine inferential support is given to the suggestion that the antidepressant action of imipramine is accomplished through a central adrenergic mechanism.

THURSDAY AFTERNOON

PSYCHOPHARMACOLOGY II

A TREADMILL DEVICE FOR STUDYING CENTRALLY ACTIVE COMPOUNDS IN RATS. Melvyn I. Gluckman. Wyeth Institute for Medical Research, Radnor, Penna.

Situations making use of conditioned behavior have been found to be sensitive indicators of the central actions of drugs. Frequently, however, these behavioral situations require long training periods to establish stable baselines. We report here a highly sensitive automatic conditioning technique that maybe used for the evaluation of drugs after as little as 3 training sessions. The technique is adaptable for testing both positive and negative motivations. Rats are trained to escape an electric shock (or obtain food reinforcement) by running on a treadmill (6" x 20"). The treadmill speed is controlled by a continuously variable motor enabling speeds up to 90 fpm. Negative motivation is provided by a charged grid (4 1/2" x 6") at one end of the treadmill. The voltage applied to the grid through a grid scrambler is continuously variable to 500 volts (60 cps., a.c.). By manipulation of the several parameters, the behavior can be varied over a wide range. D-amphetamine (1 mg/kg, i.p.) and chlorpromazine (2 mg/kg, i.p.) have opposite effects in the shock avoidance situation. Amphetamine practically eliminates shock acceptances while chlorpromazine increases them 10 to 20 fold.

A QUANTITATIVE PROCEDURE FOR ASSESSING APPETITE DEPRESSANT ACTIVITY OF DRUGS. Adolph P. Roszkowski and Nancy M. Kelley*, McNeil Laboratories, Inc., Fort Washington, Pa.

In an endeavor to assess drugs for their capacity to depress appetite, it was found that albino rats are extremely fond of beef broth (0.75% solution of Bacto-Beef Broth in 0.9% NaCl) and can be trained to consume this material voraciously when presented to them in graduated tubes. Satiation occurred in 15 minutes. This was a discriminatory feeding act and therefore a true index of appetite and not of hunger, since these animals had access to water and normal rat diet ad libitum. A total of 66 rats (Sherman) was usually divided into six equal groups and drug was administered orally to five of these groups while the sixth group received the solvent control one hour prior to broth administration. The amount of broth consumed was measured and expressed in terms of ml/kg. The results were analyzed statistically by two procedures. Initially the drug groups were compared to the control group for depression of broth consumption by the analysis of variance procedure. The animals could also be compared with respect to depression of broth consumption on an "all or none" basis, using conventional probit transformation procedures. Estimates of ED_{50}'s in mg/kg, p.o., (with 95% confidence limits) for various drugs were the following: dextroamphetamine, 7.2 (4.2-12); methamphetamine, 7.5 (5.2-11); phenmetrazine, 74 (52-105); d-3,4-dimethyl-2-phenylmorpholine HCl, 71 (41-123).

WHITE RATS AS SUBJECTS FOR ANOREXIC TESTS. George A. Emerson. Department of Pharmacology & Toxicology, Univ. of Texas Medical Branch, Galveston.

Female white rats weighing 200-300 gm are suitable for testing effects of anorectic agents, if treated twice daily with adequate oral doses for 10-20 days. Non-specific loss of weight as through systemic toxicity may be avoided by using a low fraction of the oral LD_{50}. Hematocrit estimations serve to indicate agents affecting water balance, and daily graphic representation of the S.E. of mean weights is useful to indicate abnormal variation in response to treatment, particularly in small groups. Tests of antagonism of anabolic effects of steroids are not as clear-cut as tests with anorexics alone, since the times of maximum action do not coincide and a polyphasic response is obtained with combined treatment. Many phenalkyl amines with less c.n.s. stimulant effect than dextroamphetamine are well tolerated when given orally, twice daily, at 0.2 mM per Kgm. Comparisons are made with acute effects on appetite of fasted dogs, among other tests.

CELLULAR AND BIOCHEMICAL PHARMACOLOGY II
Bausch and Lomb Lecture Hall

METABOLISM OF ETHANOL. M. Samir Amer* and Martin P. Schulman.* Dept. of Pharmacol., Univ. of Ill. Coll. of Med., Chicago, Ill.

When rat liver homogenate containing malonate or fluoroacetate was incubated with ethanol-1-C^{14}, unidentified material that released C^{14}-acetaldehyde (AcH) in acidic $FeCl_3$-$FeSO_4$ was found in the deproteinized filtrate (Fed. Proc. 20, 82, 1961). This material has been identified as a mixture of pyruvic (Pyr) and lactic (Lac) acids since: (1) Pyr and Lac coincided with the C^{14} zones on paper chromatograms; (2) Pyr 2,4-dinitrophenylhydrazone (Pyr 2,4D), obtained after adding Pyr carrier to the filtrate, contained C^{14}; (3) after adding carrier Lac and Pyr and oxidizing Lac to Pyr by Fenton's reagent, the isolated Pyr 2,4D accounted for all C^{14} in filtrate. Five recrystallizations and alumina chromatography did not decrease C^{14} in Pyr 2,4D. AcH could only arise from C_2 and C_3 of Pyr and Lac. This was confirmed by degrading Lac by Ce^{+4} after adding Lac carrier to the filtrate; 85% of C^{14} in Lac resided in C_2. The results cannot be explained by prior conversion of ethanol-1-C^{14} to acetate-1-C^{14} since the latter must traverse the citric acid cycle in order to label Lac and can only label C_1. Since only 4% of C^{14} in Lac resided in C_1, the conversion of ethanol-1-C^{14} to Lac and Pyr must have proceeded without participation of the cycle, probably by an unidentified carbon dioxide fixation reaction. (Supported by PHS MY4559.)

THE EFFECT OF CHLORPROMAZINE ON RELEASE OF NEUROHUMORS IN VITRO. Paul S. Guth and Andrew G. Finlay.* Dept. of Pharmacology, Tulane University, New Orleans, Louisiana

Chlorpromazine (CPZ) has the ability to affect permeability in a wide variety of biological systems. This permeability effect has been implicated as the mode of action of CPZ. If the implication is correct, then one ought to be able to show an effect of CPZ on membranes found in the brain. Actions by CPZ on the blood brain barrier, isolated brain mitochondria and, in preliminary experiments, isolated cerebral hemispheres are recorded. Another membrane, especially interesting because it is unique to the nervous system, is that of the so-called "synaptic vesicle." This particle may be physically isolated and caused to release its content of neurohumors by a variety of means. CPZ in concentrations between 5×10^{-4} and 5×10^{-6} partially inhibits the release of acetylcholine produced by relatively mild means such as osmotic dilution. However, when more membrane-damaging releasing methods (greater dilution or incubation at 37° C.) are used, CPZ no longer inhibits indicating that an intact membrane is necessary for CPZ's action. Regardless of concentration the mean inhibition of release by CPZ was 40% and rarely exceeded 60% possibly indicating two species of neurohumor within the particle. (Supported by USPHS Grant #MY4357)

THE RELEASING ACTION OF α-METHYL-3-HYDROXYPHENYLALANINE (α-METHYL META TYROSINE). S.M. Hess. National Heart Inst., Bethesda, Md.

α-Methyl-3-hydroxyphenylalanine (αMMT) a potent aromatic L-amino acid decarboxylase inhibitor in vivo and in vitro is capable of reducing tissue levels of serotonin, dopamine and norepinephrine in animals. Evidence is presented in this report that this agent causes the depletion of norepinephrine by an impairment of the latter's binding mechanism which leaves the storage sites with a persistent inability to retain newly formed norepinephrine. D,L-β-H^3-norepinephrine was administered to guinea pigs either before or after they had received αMMT and the labeled compound remaining in the heart four hours later was compared with control animals which had received the labeled compound only. Both regimens of treatment produced marked reduction of the administered hormone in the animals treated with αMMT indicating that the labeled catecholamine was able to enter but could not be held by the tissue. Further this work demonstrates that the binding mechanism of serotonin and dopamine are distinct from that of norepinephrine, since the latter compound remained in a depleted state for an extended period after both serotonin and dopamine had returned to normal levels.

COMPETITIVE INHIBITION OF DIHYDROXYPHENYLALANINE (DOPA) DECARBOXYLASE IN VITRO. E.C. Griesemer*, R.M. Fleming*, W.J. Hartman*, and W.C. Clark, (VA Hosp., Sepulveda and Med. Ctr., U. Calif., Los Angeles.).

45 compounds were studied as hog kidney DOPA decarboxylase inhibitors. Of those studied, 19 gave no inhibition, 10 gave less than 20% and 16 gave from 20% - 93% inhibition. Quinoid inhibition and enzyme denaturation were avoided by addition of glutathione and cysteine (non-inhibitors) to the reaction mixtures. The best inhibitors have the structure R-CH=CH-CO-R' where R is 3-OH phenyl, 3,4-diOH phenyl, 5-OH indole and R' is OH, o-alkyl, or aryl. The position of the hydroxyl group on the ring determines the strength of inhibitory action with the 3,4-position being the most effective. 30 min. incubation of enzyme and inhibitor before substrate addition increased inhibition 2½ times that of non-incubated samples. Inhibitor molarity is expressed relative to that of substrate (R.M.). Some of the more active compounds tested are: 2',3,4-trihydroxy-4'-acetoxy chalcone, 93% (0.01R.M.), 1-(5-hydroxyindolyl-3)-2-(3-carboxy-4-carboxybenzoyl ethylen, 86% (0.1 R.M.); 3', 4', 7,8-tetrahydroxyflavanone 60% (0.1 R.M.); and α-methyl-3, 4-dihydroxycinnamic acid 55% (0.1 R.M.). The phenylalanine and indole derivatives tested were generally inactive. (Supported by: Nat. Assoc. Mental Health, N.I.H., Am. Heart Assoc., Army Chem. Ctr.).

EFFECT OF 5-HYDROXYTRYPTAMINE (5-HT) ON GLYCOLYSIS IN LAMELLIBRANCH GILL. Kenneth E. Moore* and Robert E. Gosselin, Dept. of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire.

It was reported previously (Milton and Gosselin, The Pharmacologist, 1960) that 5-HT stimulates endogenous respiration and anaerobic acid production in the gill of Mytilus edulis. To study further the effects of 5-HT on the metabolism of ciliated epithelium, aerobic and anaerobic glycolysis were determined in the excised gill of Modiolus demissus and Mytilus edulis. Under aerobic conditions rates of glycogen breakdown and of lactic acid production were low. When 5-HT (10^{-5} - 10^{-6} M) was added, the lactic acid production was unaffected and the glycogen breakdown enhanced only slightly; however, the oxygen consumption was increased markedly. The gills exhibited a well-developed Pasteur effect. When incubated anaerobically 5-HT accelerated the production of lactic acid and the degradation of glycogen. LSD mimicked but brom-LSD inhibited the 5-HT effects. In an effort to localize the glycolytic action of 5-HT, gill phosphorylase was measured. The phosphorylase a content (50-65% of total) and total phosphorylase activity were not influenced by prior incubation of the excised gills in 5-HT.
(Supported by NSF Grant G 14248 and PHS Grant RG 5145).

TRANSFER OF PHENOLSULFONPHTHALEIN (PSP) AND INULIN FROM CEREBROSPINAL FLUID (CSF) TO BLOOD. Leon D. Prockop*, Lewis S. Schanker, and Bernard B. Brodie. National Heart Institute, Bethesda, Maryland.

Previous work from this laboratory has shown that inulin, sucrose, mannitol, and dextran, substances which enter the CSF at extremely slow rates when administered intravenously, all pass readily at similar rates from CSF to blood after injection into a lateral cerebral ventricle. The mechanism of the essentially one-way transfer appears to be a filtration of CSF across a sieve-like boundary thought to be located at the arachnoid villi. When PSP and tritium-labeled inulin were injected into the ventricle of anesthetized rabbits, the dye passed from CSF to blood much more rapidly than the saccharide. For example, after 6 hours, only 0.18% of the injected dose of PSP, but 12% of the inulin, remained in 1 ml of CSF. Moreover 45% of the PSP and only 10% of the inulin were recovered in the urine after 2 hours, the values rising to 90% and 43% after 6 hours. Similar results were obtained on injecting PSP and inulin into the cisterna magna. The rapid passage of PSP from CSF to blood suggests that the dye is transferred by a specialized transport process possibly similar to that recently described in the goat by Pappenheimer et al. (Am. J. Physiol., 200:1, 1961).

BIOCHEMICAL EFFECTS OF 6-AZAURACIL ON TRYPANOSOMA EQUIPERDUM. R. J. Rubin*, J. J. Jaffe* and R. E. Handschumacher*. Dept. of Pharmacology, Yale Univ. Med. School, New Haven.

Azauracil (AzU) but not azauridine (AzUR) prolongs the survival time of mice infected with Trypanosoma equiperdum; AzU is about 100 times more potent as an inhibitor of orotate utilization by trypanosomal suspensions than AzUR (Jaffe, Biochem. Pharmacol., in press). Recent experiments with suspensions of these protozoa have demonstrated that both AzU and AzUR enter these organisms readily. Following entry, AzU is converted to what appears to be azauridylic acid, on the basis of ion-exchange and paper chromatography. AzUR failed to give rise to such a derivative, suggesting that T. equi. lacks an AzUR kinase but can transform AzU to the 5'-ribonucleotide by condensation with pyrophosphorylribose-5-phosphate (PRPP). Orotidylate-$C^{14}OOH$ is readily decarboxylated by non-fortified cell-free extracts but orotate-$C^{14}OOH$ is not until PRPP is added. The PRPP condensing enzyme and the decarboxylase are found in the particulate fraction and sediment at 850 x g. The decarboxylation of orotidylate with or without PRPP in the cell-free system is completely inhibited by 0.01 μmoles of azauridylic acid/ml but AzU required PRPP for inhibition; AzUR (2 μmoles/ml) was inactive as an inhibitor under either condition. Thus, these parasites are fundamentally different from mammalian cells in their anabolism of 6-AzU.

HYDROXYETHYLATION OF ALBUMIN FROM NORMAL AND TUMOR-BEARING RATS. Wesley C. Starbuck* and Harris Busch. Depts.of Pharmacology and Biochemistry, Baylor Univ. College of Medicine, Houston, Texas.

Evidence has been presented for uptake of intact albumin into neoplastic cells (Busch et al., Cancer Res., 21: 371, 1961). To test the feasibility of linking chemotherapeutically active groups to intact protein, albumin was hydroxyethylated with excess ethylene oxide for 24 hours. At pH 3 and above, unmodified tyrosine and lysine residues were reduced to trace amounts, and histidine was reduced by more than 90% above pH 5. Four new peaks, B-I to B-IV, were eluted from the basic column of the amino acid analyzer. The first three were eluted prior to lysine and the fourth between lysine and histidine. At pH 7, HEA contained less than 0.5% of B-I and B-II, 7-8% of B-III and 1-1.5% of B-IV. HEA (pH 7) from tumor-bearing rats contained 2% of B-I and B-II, and only 1.5% of B-III. After labeled HEA was injected into tumor-bearing rats, the S.A. of proteins of the whole homogenate of tumor, liver, spleen, and intestine were 16, 12, 12 and 8 respectively. After injection of labeled normal albumin, the S.A. of proteins of the whole homogenate of the tumor was more than twice that of other tissues. These data indicate that modification of the albumin under these conditions results in loss in the specificity of uptake into tumor cells, and that a difference may exist between albumin of tumor-bearing and normal rats.

BIOLOGICAL ACTIVITY OF DIHYDROAMINOPTERIN. C. A. Nichol, M. T. Hakala* and S. F. Zakrzewski*. Dept. of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, N. Y.

The antimicrobial activity of tetrahydroaminopterin, as prepared by Kisliuk (Nature 130, 584, 1960), was found to be due primarily to a contaminant which was identified as dihydroaminopterin by paper chromatography. Dihydroaminopterin was prepared by reduction of purified aminopterin with sodium dithionite. Two compounds, presumably isomers, were separated by differential solubility at about pH 5.0. A product which gave a single blue fluorescing spot on paper chromatograms had biological activity and by iodine titration appeared to be a dihydro derivative. Dihydroaminopterin and aminopterin were equally potent as inhibitors of folic acid reductase from chicken liver or Streptococcus faecalis, 8043; tetrahydroaminopterin appeared to be only 1/5 as potent as an inhibitor of the enzyme from liver. Dihydroaminopterin was 120 times more inhibitory than aminopterin for the growth of Pediococcus cerevisiae, 8081. The compounds were equally inhibitory for S. faecalis, 8043, and a subline of P. cerevisiae, 8081/S, which has greater capacity than the parent line, 8081, to concentrate folic acid and aminopterin within the cells. Each organism was grown in media containing folinic acid. Dihydroaminopterin appears to differ from aminopterin with regard to cellular uptake.

THE EFFECTIVENESS OF THE CHEMOTHERAPY OF MOUSE TUMORS AS A FUNCTION OF DOSE, SCHEDULE AND ROUTE OF DRUG ADMINISTRATION. M. Blair, J. Miller*, R. Porter* and C. J. Kensler. Life Sciences Division, Arthur D. Little, Inc., Cambridge, Mass.

An extensive series of experiments were undertaken using six drugs (6 MP, 6 MPR, HN_2, Thio-TEPA, cyclophosphamide (Cytoxan) and 1-methyl-1-nitroso-urea (NMU) and mice bearing either Leukemia L-1210 or Carcinoma 755. Drug therapy was initiated either 24 hours after transplantation or five days after transplantation. The compounds were given by the oral, intravenous and intraperitoneal routes by six schedules ranging from twice a day to every sixteenth day. Five doses graded by a fixed logarithmic interval were administered to each of these schedules. Toxicity was evaluated by the incidence of mortality, body weight loss and suppression of the white blood cell count. With several of these agents the infrequent administration of large doses was more effective than the frequent administration of the same or smaller doses. For example, 40 day survivals ("cures") in L-1210 mice were only obtained in those groups receiving the infrequent therapy (every 4-16 days). At the other extreme, the less effective agent NMU was slightly more effective when given at frequent intervals. Data indicating the effects of the dose schedule and route of administration on the various therapeutic indices will be presented.

PHARMACOLOGY AND ANTISEPTIC EFFECTS OF TWO PROPOCTAMINE COMPOUNDS. Michael G. Mulinos and Benjamin D. Erger.* Commercial Solvents Corp., New York City and State Univ. of New York, Downstate Medical Center, Brooklyn.

Propoctamine is 2-methyl-N^1,N^3-bis (2-ethylhexyl)-1,2,3-propane triamine and methyl-propoctamine is the N^1-methyl derivative. They have alkaloidal properties which form water soluble salts with mineral and organic acids, and possess broad-spectrum antimicrobial characteristics, including activity against fungi and insect grubs. They are strongly substantive on skin and various textiles, adhering firmly and resisting numerous washings. Rat oral LD_{50}, 800 and 1000 mg. per Kg.; I.P. LD_{50}, 100 and 115 mg. per Kg., respectively. Mucous membranes are variously irritated by the propoctamines, the most sensitive being the eyes and bronchi. The stomach appears less sensitive, as are the mouth and gums. The skin is not irritated and there is no allergenicity. Clinically, a 1.0% ointment is effective against superficial bacterial infections of the skin and infestations of the scalp and skin, except Monilia. The propoctamines are slowly absorbed from the skin when applied as ointments or oily solutions in high concentrations, and elicit low toxicity in animals.

NEUROPHARMACOLOGY II
Morey 321

THE EFFECTS OF CNS STIMULANTS UPON PENTOBARBITAL DEPRESSION IN DOGS. A. Kandel, R. B. Miller*, C. A. Leonard* and E. J. Fellows, Smith Kline and French Laboratories, Philadelphia, Pennsylvania

The character of the stimulant activity of certain anorexigenic and antidepressant agents has been amplified by means of their effect upon the depth of pentobarbital depression in dogs. The amount of anesthetic injected is that which produces loss of prone position, flaccid paralysis of fore-and hind-limbs, and absence of head and body movements in 95 percent of the animals. The stimulants administered orally at suitable intervals and doses prior to injection of the pentobarbital prevent one or more of these effects. Under these conditions d-amphetamine appeared to be the most potent of the compounds tested. The others are listed in order of decreasing potency: pipradrol, diethylpropion, and phenmetrazine. This order is not sustained when ratios of the pentobarbital antagonism ED_{50} to the anorexia ED_{50} for the different compounds are compared: no significant differences among these compounds could be observed in this regard. Caffeine prevents the characteristic pentobarbital depression at doses markedly lower than those influencing appetite. On the other hand, p-trifluoromethylamphetamine while producing anorexia in dogs does not prevent pentobarbital depression at doses four-times the anorexia ED_{50}.

THE ANALEPTIC ACTION OF ADRENERGIC NEURONE BLOCKING AGENTS IN BARBITURATE DEPRESSION. Alexander H. Friedman* and A. S. Kulkarni* Dept. of Pharmacology and Toxicology, The University of Wisconsin Medical School, Madison 6, Wis.

The marked resistance of the myocardium of the dog pretreated with bretylium tosylate to lethal doses of pentobarbital suggested the possibility that adrenergic neurone blocking agents could counteract the depression induced by barbiturates. This hypothesis was tested by determining the effect of adrenergic neurone blockers, as well as other types of adrenergic blocking agents, on the duration of sleep induced in mice by sodium pentobarbital. Groups of non-fasted male mice (8-16 animals/group, weighing 20-30 grams) were injected I. P. with 65 mg/kg of sodium pentobarbital. Fifteen minutes later each group received I. P. one of the following agents: Bretylium tosylate (B), 50 mg/kg; S. K. F. 5377-C (TM-10), 7.5 mg/kg; S. K. F. 6890-A (β-TM-10), 7.5 mg/kg; Dibenzyline HCl (D), 5 mg/kg; dichloroisoproterenol (DCl), 2 mg/kg; dihydroergotamine methanesulfonate (DHE), 1 mg/kg. Sleeping times were significantly shortened by B, TM-10, β-TM-10 and DCl but not by D or DHE. Reserpinization (2.5 mg/kg, I. P.) 19-24 hours prior to testing prevented the shortening of sleeping time induced by B, TM-10, β-TM-10 and DCl.

NEUROPHARMACOLOGY OF dl -α-METHYL-p-TRIFLUOROMETHYLPHENETHYLAMINE HYDROCHLORIDE (SKAF No. 7410-A). C.A.Leonard*, T. Fujita*, D.H.Tedeschi, and E.J.Fellows, Smith Kline and French laboratories, Philadelphia, Pennsylvania.

SKAF No. 7410-A was evaluated for anorexigenic activity and concomitant effects in rats, dogs and monkeys. In the anorexia tests 7410 was approximately 3/8 as potent as d-amphetamine in the rat and 1/7 as potent in the dog and monkey. Dogs and monkeys receiving 7410 did not show increased motor activity even at maximum tolerated dosages. In other tests 7410 was found to be approximately equal in potency to d-amphetamine in producing a blockade of the conditioned avoidance response in rats. Analgesia and in vivo inhibition of monoamine oxidase were not manifested in the rat. Anticonvulsant effects in the mouse maximal electroshock test were present but only in doses in the order of the LD_5. No antagonism to pentobarbital-induced depression in rats and dogs was observed with 7410. The oral LD50's compared with those of d-amphetamine showed that 7410 is only 1/3 as toxic in the rat and 1/6 in the mouse. In the unanesthetized dog only a slight hypotensive effect was noted and EKG effects were similar to those of d-amphetamine. Glucose tolerance studies in dogs showed no difference from d-amphetamine and controls.

AUTONOMIC AGENTS THAT CAUSE DEATH AFTER SUPRA-MAXIMAL ELECTROSHOCK IN MICE. C. D. Hendley, T. M. Mikiten*, and S. Irwin. Dept. of Neuropharmacology, Schering Corp., Bloomfield, N.J.

In some strains of mice there is a high mortality from respiratory depression shortly after the tonic extensor component (TE) of maximal electroshock seizures. This does not appear to occur in CF#1 male mice, 18-24 grams (40 ma., 0.2 sec., AC stimulus). The animals die under these conditions, however, if pretreated i.p. with dopamine (100 mg/kg) or iproniazid followed by dopamine (50 mg/kg). The same is observed after atropine or scopolamine alone (1 mg/kg), or other anticholinergics including scopolamine methylbromide, atropine methylnitrate, JB-329, or propantheline. Dibenzylene (2.5 mg/kg) reduces the mortality after dopamine; arecoline (10 mg/kg) or physostigmine (3 mg/kg), the mortality after atropine. Anticonvulsant drugs protect if they block the TE component of the seizures. Artificial respiration, until normal breathing returns, also prevents death. The data suggest that a mechanism involving catechol amines in the brain may delay recovery of the respiratory center after electroshock, and that a cholinergic mechanism may have the opposite effect. Thus, if the balance between these is upset, respiration may fail after TE. The extent to which peripheral or central mechanisms are involved is under investigation.

SENSITIVITY OF THE NICTITATING MEMBRANE AFTER DENERVATION AND AFTER VARIOUS DRUGS. U. Trendelenburg and N. Weiner. Dept. of Pharmacology, Harvard Medical School, Boston, Massachusetts.

The sensitivity of nictitating membrane of spinal cats to norepinephrine (NE), tyramine (TYR) and acetylcholine (ACH) was studied after the following procedures: (a) chronic denervation, (b) chronic decentralization, (c) pretreatment with single, large dose of reserpine (3 mg/kg 24 hr prior to experiment), (d) 14 daily injections of 0.1 mg/kg reserpine, (e) 7 days of 10 mg/kg TM 10 per day, and (f) 7 days of ganglion blockade with chlorisondamine (2-5 mg/kg, twice daily). Supersensitivity to NE and ACH was observed in all groups of cats with the exception of (c); subsensitivity to TYR appeared in (a), (c) and (d), supersensitivity to TYR in (b), (e) and (f). Catecholamines in heart, aorta, iris, nictitating membrane and adrenal medulla were measured by fluorimetric method; they were normal in group (f), slightly reduced in (e) and severely reduced in (c) and (d). There is thus no relation between depletion of NE stores and supersensitivity to NE, which seems to be the result of interruption of tonic impulses for 7 days. Subsensitivity to TYR is related to depletion of NE stores. (Supported by USPHS grants B-1713 and B-2947 and US AF 41(657)-197.)

DIFFERENTIAL EFFECTS OF DILANTIN ON VARIOUS COMPONENTS OF THE PYRAMIDAL RESPONSE. Baruch Blum*. Montreal Neurol. Inst., Montreal, Canada.

Motor cortex stimulation produces in the pyramidal tract an electrical response, composed of an initial "D wave", supposedly the direct response of the excited cells, and longer latency "I waves", thought to be synaptic, resulting from re-excitation of other Betz cells through collaterals of interneurones. Sensorimotor cortex or Thalamic VL stimulation produces "relayed" pyramidal responses. Different motor cortex cells appear to be involved in the elaboration of these responses. The anti-epileptic drug diphenylhydantoin (Dilantin) applied topically depressed all the above responses, but with regulation of dosage, it depressed first the D wave exerting later a stronger depression on the I waves, leaving almost unaffected the other responses. I.V. Dilantin 18 mg/kg markedly depressed the I wave with moderate effect on the D wave, whereas 24 mg/kg markedly depressed both. These dosages left unaffected the sensorimotor elicited response with small effect on the relayed thalamic-elicited ones. Larger doses (30 mg/kg), used in studies on after-discharges, depressed indiscriminantly all the above responses. It was concluded that the differential effect of the drug as shown here may be related to its specificity as a non-hypnotic, anti-epileptic drug. Supported by The National Research Council of Canada.

EFFECT OF ELECTRICAL STIMULATION ON THE NEURAL SYNTHESIS OF NORADRENALINE FROM L-TYROSINE-C^{14}. W.G. Clark, F.J. Kotichasy, H.F. Schott*, D.T. Masuoka*, and W. Drell*. VA Hosp., Sepulveda and Med. Ctr., U. Calif., Los Angeles.

Paired thoracic sympathetic chains of cats were extirpated under pentobarbital, placed in specially designed chambers at 37° and perfused with Krebs solution containing uniformly labelled L-tyrosine-C^{14}. One nerve was continually stimulated (0.5-0.8 volts, 30 C.P.S.) and the other used as an unstimulated control. After 2 to 3 hours the nerves were removed from the solution and the tissue extract and perfusion fluid separately analyzed by chromatography on alumina, and CG-50 resin. C^{14}-noradrenaline but no adrenaline and little or no dopamine appeared regularly in the tissue fraction. An as yet unidentified non-catechol amine appeared in the fluid fraction. The extract of the stimulated nerve regularly yielded 2 to 5 times as much labeled noradrenaline as that of the unstimulated nerve, and about twice as much total radioactivity. Similar results were obtained when the nerves were pretreated with C^{14}-tyrosine and then immersed in plain Krebs solution before commencing the stimulation. (Supported by N.I.H., Am. Heart Assoc. and Nat. Assoc. Mental Health).

MODIFICATION OF AFFERENT INTERACTION PATTERNS BY CHLORPROMAZINE, MEPROBAMATE, MORPHINE AND PENTOBARBITAL. C.L. Mitchell*, S.D. Nelson* and K.F. Killam. Stanford Univ. School of Med., Palo Alto, Calif.

In cats surgically prepared under ether anesthesia and subsequently immobilized with gallamine triethiodide responses were evoked in mesencephalic, thalamic, rhinencephalic and neocortical structures by pairing of photic and tooth pulp stimulation. Stimulus trains, programmed to be presented at random intervals of 50 to 95 seconds, consisted of 3 flashes of light 100 msec. apart followed in 350 msec. by a single stimulus to the tooth pulp (TPS). 25 control responses to the flash sequence alone followed by 100 or more responses to the flash plus TPS were elicited before drug administration. Evoked responses to TPS decreased with repetition. Chlorpromazine at 1, 2, and 5 mg/kg, pentobarbital at 5, 10 and 15 mg/kg, meprobamate at 10, 20 and 50 mg/kg and morphine sulfate at 0.5, 1, and 2 mg/kg were administered intravenously. In general, all drugs enhanced responses to photic stimulation in lateral geniculate and optic cortex. Responses to TPS were differentially affected by the various drugs in the specific and nonspecific systems. (Supported by NIH grants MY3241 and MY3374)

THURSDAY AFTERNOON

NEUROPHARMACOLOGY II

A TECHNIQUE FOR THE CLASSIFICATION AND COMPARISON OF DRUG EFFECTS ON THE CAT WITH CHRONICALLY IMPLANTED ELECTRODES. Zola P. Horovitz* and May-I Chow*. The Squibb Institute for Medical Research, New Brunswick, New Jersey.

A rating scale for the simultaneous evaluation of behavior and E.E.G. recording was developed to classify and compare the effects of drugs acting on the central nervous system. A brief description of the method of implanting permanent electrodes in the cat and of the recording and rating procedure will be given. The rating scale was devised so that, in the normal animal, the behavior and E.E.G. ratings tended to be numerically equal (closely associated). Any "dissociation" phenomena (such as that produced by atropine) was thus reflected in a divergence of the ratings. "Dissociation" of behavior and E.E.G. was demonstrated for atropine, Ditran and tetrahydroaminacrin. In contrast, imipramine showed no "dissociation" and produced in fact behavioral and E.E.G. depression similar to that seen with chlorpromazine and triflupromazine.

THE PSEUDAFFECTIVE RESPONSE TO INTRA-CORONARY INJECTION OF BRADYKININ AND OTHER ALGESIC AGENTS. Frank Guzman*, C. Braun*, and R.K.S. Lim. Miles Lab. Inc., Elkhart, Indiana.

We have reported (J. Physiol. Lond., 155, 13P, 1961) that the intra-arterial injection of chemical agents into somatic, abdominal and internal carotid vessels evoke Woodworth and Sherrington's pseudaffective reflex, consisting of vocalization, blood pressure change, hyperpnea, etc., in the chloralose dog and cat. Since these agents produce the same response as electrical and mechanical nociception they may be assumed to stimulate the same nociceptive receptors. These observations have now been extended to the cardiac vessels. Injections of natural and synthetic bradykinin (1.5-2.5 μg), acetylcholine (500 μg), histamine (100 μg), 5-hydroxytryptamine (100 μg) and KCl (37.5 mg) into the left coronary artery also evoke the pseudaffective response. The same agents in the same doses injected in the vena cava and descending aorta at the level of the heart failed to produce any response. Injections into the pulmonary artery were also negative except in the case of 5-hydroxytryptamine. The depressive action of KCl on the heart probably accounts for its general lack of effectiveness except at near lethal doses. These results show that the heart contains nociceptive receptors of the same type as occurs in other regions of the body.

FRIDAY MORNING

DRUG METABOLISM
Bausch and Lomb Lecture Hall

DETERMINATION OF MONOCROTALINE IN BIOLOGICAL MATERIAL. Edwin I. Goldenthal*. Div. of Pharmacology, Food and Drug Admin., U.S. Dept. of Health, Education, and Welfare, Washington, D.C.

The legume, Crotalaria spectabilis, has been used for many years to improve soils in the southeastern United States. Its seeds are toxic in laboratory and domestic animals at dietary levels as low as 0.01%. The toxic principle has been shown to be the alkaloid monocrotaline. Recent contamination of food products with these seeds has led to the following study of the alkaloid. Monocrotaline was extracted from C. spectabilis seeds and obtained as a pure crystalline material. A sensitive method for the estimation of monocrotaline in biological material has been developed using a modification of the methyl orange colorimetric method. Monocrotaline was isolated from biological material by extraction into ethylene chloride at pH 7.5. The pH of the initial extraction appears to be critical with the maximum extraction occurring between pH 7 and 8. The recovery of monocrotaline from tissues and urine is about 95%. This procedure permits the estimation of 2 μg. of monocrotaline. The presence of the alkaline hydrolysis product of monocrotaline, retronecine, does not have any effect on color intensity. By the use of this method, preliminary results indicate that approximately 50% of a 150 mg/kg oral dose in rats is excreted in the urine in 24 hours, 25% within the first 4 hours.

MECHANISM OF MEPROBAMATE TOLERANCE IN THE RAT. Barrie M. Phillips*, Tom S. Miya and George K. W. Yim*. Dept. of Pharmacology, Purdue University, Lafayette, Indiana.

The production of tolerance to meprobamate in rats has been reported previously (Miya, et al., Pharmacologist, 2, 92, 1960). Male Holtzman rats were used throughout the current studies. Treated rats received daily doses (IP) of 270 mg/Kg of meprobamate, while controls received equivalent volumes of 4% acacia daily. All studies were performed with rats treated for 35 days. Initial brain and blood levels in tolerant and control rats are the same, thus access of the drug to the CNS is not altered. However, the levels decreased at a significantly greater rate in tolerant rats. The biological half-life of C^{14}-meprobamate in tolerant rat brain is 1.87 hours; in control rat brain 3.69 hours. A similar pattern was seen in muscle and fat, indicating that storage in an inactive site is probably not a factor. Urinary excretion studies reveal that while both tolerant and control animals excrete essentially the same amount of C^{14} in 24 hours, tolerant rats excrete a significantly greater amount of C^{14} during the first 5 hours. Tolerant rats excrete less unchanged meprobamate in urine than controls (8.6 and 14.6% respectively) in 24 hours. These findings suggest that tolerance to meprobamate in the rat occurs as the result of an increased rate of drug metabolism. Supported by NIMH Grants M-2405 and MF-12,151.

THE EFFECT OF PRETREATMENT WITH PHENYLBUTAZONE ON PLASMA LEVELS OF AMINOPYRINE IN MAN. Peter G. Dayton, W. Chen*, P. Blaber*, and J. J. Burns. N.Y.U. Res. Serv., Goldwater Mem. Hosp., New York, N.Y.

Pretreatment with phenylbutazone increases the rate of metabolism of aminopyrine in rats (Conney, A. H. et al. J. Pharm. and Exp. Thera. 130, 1, 1960). To test whether pretreatment with phenylbutazone causes similar effects in man, 7 human subjects were administered 800 mg of aminopyrine i.v. and plasma levels of aminopyrine were determined. Four to 21 days later the same subjects were treated with 400-800 mg of phenylbutazone p.o. in divided doses for 7-10 days. On the last day of phenylbutazone dosage, the subjects were again administered 800 mg of aminopyrine i.v. and plasma levels of aminopyrine were determined. The results indicate that pretreatment markedly decreased the level of aminopyrine, suggesting the possibility of an increase in the rate of metabolism. The implications of these findings will be discussed.

METABOLISM OF ISOXSUPRINE-C^{14} IN THE RAT. John A. LaBudde* and Paul D. Joiner*. Dept. of Pharmacology, Research Center Mead Johnson & Co., Evansville, Indiana.

The tissue distribution, excretion and biotransformation of C^{14}-labeled isoxsuprine, 2-(3-phenoxy-2-propylamino)-1-(p-hydroxyphenyl)-1-propanol, have been studied in the rat. One hour after intravenous administration of the labeled drug, 70% of the radioactivity was found in the small intestine and contents, while at this time the specific activities of blood and other tissues had fallen to relatively low values. Within 4 hours after dosage, in vivo or in the isolated perfused rat liver, up to 90% of the administered radioactivity appeared in the bile, none in the form of free isoxsuprine. The rapid disappearance of free isoxsuprine from tissues is apparently the result of extensive biotransformation by the liver followed by biliary excretion of the metabolites. However, urinary excretion of radioactivity was found to be high at later time periods, indicating that the metabolized drug undergoes enterohepatic circulation. Five conjugated metabolites of isoxsuprine, in addition to its conjugate with glucuronic acid, were isolated from rat bile by paper and column chromatography. Formation of these five metabolites was greater in the isolated perfused rat liver than in the whole animal.

FRIDAY MORNING

DRUG METABOLISM

STUDIES OF N-DEALKYLATION OF SOME AROMATIC SULFONAMIDES. Edward H. Wiseman*, Eric C. Schreiber* and Rex Pinson, Jr.*, Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Conn.

Many compounds with a free-SO_2NH_2 group are known to inhibit the enzyme carbonic anhydrase. Substitution on the nitrogen atom destroys this power. Reports (Maren, J. Pharmacol. 117, 385 (1956), Lund et al, Acta pharmacol. et toxicol. 16, 297 (1960)) indicate that N-alkyl-sulfonamides regain activity in vivo, an N-dealkylation step being postulated. Such activation towards carbonic anhydrase by N-dealkylation brings into question the role of N-demethylation in the action of the 2-methyl thiazide diuretic, polythiazide. (P-2525; 2-methyl-3(2,2,2-trifluoroethylthiomethyl)3,4-dihydro-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide). That the 2-methyl group of P-2525 and several of its congeners is not removed in vivo, was shown as follows: Rats receiving 2(C^{14})-methyl-3(2,2,2-trifluoroethylthiomethyl)-3,4-dihydro-6-chloro-7-(C^{14})-methylsulfamyl-1,2,4-benzothiadiazine-1,1 dioxide, (P-2400) orally, excrete 2(C^{14})-methyl-P-2525 and 3-[(C^{14})-methylsulfamyl]-4-amino-6-chlorobenzenesulfonamide, (P-2400), plus expired $C^{14}O_2$. The absence of expired $C^{14}O_2$ after administration of 2-(C^{14})-methyl-P-2525 showed that the $C^{14}O_2$ stemmed entirely from the 7(C^{14})-methyl group in P-2400. This work was confirmed in the dog (P-2400 100 mg/kilo I.V.). Other benzene sulfamyl derivatives have been studied.

1-AMINO-2-NAPHTHYL GLUCURONIDE, A METABOLITE OF EXT. D&C RED NO. 14 (1-XYLYLAZO-2-NAPHTHOL) AND CITRUS RED NO. 2 (2,5-DIMETHOXYPHENYLAZO-2-NAPHTHOL). J. L. Radomski, Dept. of Pharmacology, Univ. of Miami School of Med., Coral Gables, Fla.

These compounds are red oil-soluble azo dyes. It has been reported by the author that both of these dyes are metabolized by conjugation and reductive fission of the azo group to 1-amino-2-naphthyl sulfate. The presence of the glucuronide of 1-amino-2-naphthol also has recently been established. 1-Xylyl-azo-2-naphthol-8-C^{14} was administered to large rats at a daily doses of 100 mg/kg for three days. Chromatographic examination of the urine of these rats revealed, in addition to seven water-soluble red metabolites and 1-amino-2-naphthyl sulfate, a bright blue-white fluorescent spot which was highly radioactive and gave a deep red color when sprayed with hexylresorcinol. This metabolite was isolated, incubated with B-glucuronidase, and an ether extraction performed. The ether extract was chromatographed revealing a spot identical in Rf and all its characteristics to 1-amino-2-naphthol, a compound which produces tumors when implanted in the bladders of mice. The identification was confirmed by spectrophotofluorometric comparison of the decomposition products. Similar experiments with Citrus Red No. 2 revealed the presence of 1-amino-2-naphthyl glucuronide in the urine of rats administered this dye as well. (Supported by Grant No. C-3859, National Institutes of Health.)

ION-EXCHANGE PAPER SEPARATION OF URINARY METABOLITES OF NORADRENALINE. George F. Bajor* and William G. Clark, (with the tech. assist. of Jack Lewis), VA Hosp., Sepulveda, and Med. Ctr., U. Calif., Los Angeles.

In studying noradrenaline-β-C^{14} metabolism in essential hypertension, a rapid method was developed for separating and quantitatively determining the labelled urinary metabolites. DL-Noradrenaline-β-C^{14} was infused I.V. and 24 hr. urines collected. 5 ml aliquots were passed through a 3 x 3 cm. column of CG-50 resin and the effluent containing the acidic metabolites evaporated in vacuo to 0.5 ml. Ten to 50λ of this was spotted on 18 x 24 in. sheets of IRA-400 ion-exchange paper (Reeve Angel type SB-2) in the acetate form, developed with 10M NH_4 OAc, pH 5, dried, cut into 1 cm. strips and counted in a liquid scintillation spectrometer in toluene phosphor. Four major radioactive peaks appear, 3,4-dihydroxymandelic acid, 3-methoxy-4-hydroxymandelic acid and two others, probably (La Brosse, et al, J. Clin. Invest. 40: 253, 1961) normetanephrine conjugate and 3-methoxy-4-hydroxyphenylglycol. The peaks are similar to those obtained from Dowex-1 columns. (Supported by L.A. County Heart Assoc., Am. Heart Assoc., and N.I.H.).

THE FATE AND EXCRETION OF d-AMPHETAMINE IN MAN. Rex Pinson, Jr.*, Josephine Chiaini* and Doris Baumgartner*, Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Connecticut.

Although the physiological disposition of amphetamine in a number of species has been investigated in some detail, studies in humans have heretofore been concerned only with the excretion of unchanged amphetamine. Other than the approximately 40% thus accounted for, the fate of the drug was unknown. The objective of this investigation was to determine the ultimate disposition of the balance of the administered amphetamine. Normal human subjects receiving, during an eight hour period, 30 mg. of d-amphetamine sulfate in three divided doses excrete 85 to 100% of the dose within 48 hours. As others have reported previously, 35-60% is excreted in the urine unchanged. The remainder is hydroxylated and excreted as p-hydroxyamphetamine. Little p-hydroxyamphetamine is excreted in the free form; most of it appears in the urine as conjugates, probably a mixture of the glucuronide and sulfate.

METABOLISM OF A GABA TRANSAMINASE INHIBITOR; AMINOOXYACETIC ACID (AOAA). G. R. Zins,* Department of Pharmacology, The Upjohn Company, Kalamazoo, Michigan.

The ability of AOAA to inhibit GABA transaminase and elevate brain levels of GABA (Wallach, D. P., Biochem. Pharm. 5, 323; 1961) and to antagonize thiosemicarbazide and methionine sulfoxamine convulsions (DaVanzo et al., This Meeting, 1960) prompted a study of the disposition and metabolism of this compound in animals. The I.V. serum half-life was 5 min. in rats while a 2 component curve with half-lives of 5 min. and 20 min. was found in dogs. Upon I.V. injection of AOAA-2-C^{14} in rats, 49%, 2.5% and 19.4% of the C^{14} appeared within 24 hours in urine, feces and CO_2 respectively; 54% of the dose appeared in the urine of dogs. AOAA-2-C^{14} appeared in highest concentration in the liver and kidney of rats and dogs. Brain levels were much lower than serum and gray matter of dog brain contained larger quantities than white. The principal urinary metabolite of AOAA in the rat and dog was glycolic acid. Smaller amount of glyoxylate and oxalate were also found. Rat liver slices aerobically degraded AOAA to a nitrogenous substance and glyoxylate which subsequently was converted to CO_2 or oxalate. Glycolate was produced by intestinal mucosa and kidney but brain slices failed to metabolize the compound.

THE EFFECT ON THE DISTRIBUTION AND EXCRETION OF SALICYLATE BY DRUGS DISPLACING THAT COMPOUND FROM PLASMA BINDING SITES. C. Davison and R.L. Strautz,* Dept. of Pharmacology, George Washington Univ. Medical School, Washington, D.C.

The in vitro competition of approximately 80 anionic compounds with salicylate for binding to crystalline bovine serum albumin has been evaluated. Nine of these, representing hydroxylated salicylates, long-chain fatty acids, aromatic sulfonic acids, coumarins and phenylbutazone derivatives, have been administered to rats and mice along with radioactive salicylate. Doses of salicylate employed have been 2, 50 and 200 mg/kg, with the competing drug at 100, 5 and 5 times that concentration, respectively. Up to five-fold increases in tissue content of salicylate have been observed and excretion during 1 hour was markedly decreased in most cases. In agreement with the findings of Anton regarding competition with sulfonamides (Fed. Proc. 20 171 (1961)), the phenylbutazone analogs are among the most potent competitors with the salicylate ion.

INFLUENCE OF 6-AMINONICOTINAMIDE ON ETHANOL AND BARBITURATE DETOXICATION. H. M. Redetzki* and F. Alvarez-O'Bourke,* Dept. of Pharmacology-Toxicology, Univ. of Tex. Med. Branch, Galveston, Tex., and Dept. of Pharmacology, L. S. U. Sch. of Med., New Orleans, La.

6-aminonicotinamide (6-AN), a powerful antimetabolite, was shown to replace nicotinamide in the DPN and TPN molecule. Enzymatic analysis of liver homogenate of mice pretreated with 10-100 mg/kg of 6-AN revealed however no significant decrease of functional DPN. Studies of the rate of ethanol oxidation in mice also failed to demonstrate impairment of DPN dependent enzymatic reactions. A specific interaction of 6-AN was found for detoxication of thiobarbiturates. A two- to threefold increase of sleeping time was observed after intraperitoneal application of thiopental and thiamylal when mice were pretreated 2-24 hrs. with 6-AN. Among other short-acting barbiturates, no appreciable change was seen with pentobarbital while the hexobarbital sleeping time was significantly increased by 6-AN. The effect of 6-AN on barbiturate detoxication apparently involves compounds which tend to concentrate readily in body fat.

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